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11

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he frontiers of cardiomyopathy *John F Goodwin* 1

Haemodynamic effects of nifedipine and propranolol in patients with hypertrophic obstructive cardiomyopathy *K Landmark, S Sire, E Thaulow, J P Amlie, S Nitter-Hauge* 19

Effects of lignocaine on bidirectional tachycardia and on digitalis-induced atrial tachycardia with block *A Castellanos, J Ferreiro, K Pefkaros, J J Rozanski, F Moleiro, R J Myerburg* 27

Influence of beta adrenergic blockade on effects of physical training in patients with ischaemic heart disease *L Vanhees, R Fagard, A Amery* 33

Scintigraphic study of relation between left ventricular peak systolic pressure and end-systolic volume in patients with coronary artery disease and normal subjects *J Watkins, R Slutsky, J Tubau, J Karliner* 39

Systolic closure of aortic valve in patients with prosthetic mitral valves *M Eldar, M Motro, S Rath, N Schy, H N Neufeld* 48

Morphometric investigations in mitral stenosis using two dimensional echocardiography *P Schweizer, P Bardos, W Krebs, R Erbel, C Minale, S Imm, B J Messmer, S Effert* 54

Evaluation of left ventricular performance during supine exercise by transoesophageal M-mode echocardiography in normal subjects *M Matsumoto, P Hanrath, P Kremer, C Tams, B A Langenstein, M Schlüter, R Weiter, W Bleifeld* 61

Transoesophageal cross-sectional echocardiography with phased array transducer system. Technique and initial clinical results *M Schlüter, B A Langenstein, J Polster, P Kremer, J Souquet, S Engel, P Hanrath* 67

Case reports
- Anomalous connection of left atrial appendage with persistent left superior vena cava *L M Gerlis, J B Partridge, G I Fiddler* 73
- Slowing of paroxysmal tachycardia with loss of functional bundle-branch block *R A Bauernfeind, B Strasberg, K M Rosen* 75
- Presystolic mitral closure sound in aortic regurgitation with left ventricular hypertrophy and first degree heart block *T A Traill, N J Fortuin* 78
- Coronary artery surgery using inverted internal mammary artery *J J Goiti, G H Smith* 81

Correspondence 83

Proceedings of the British Cardiac Society 87

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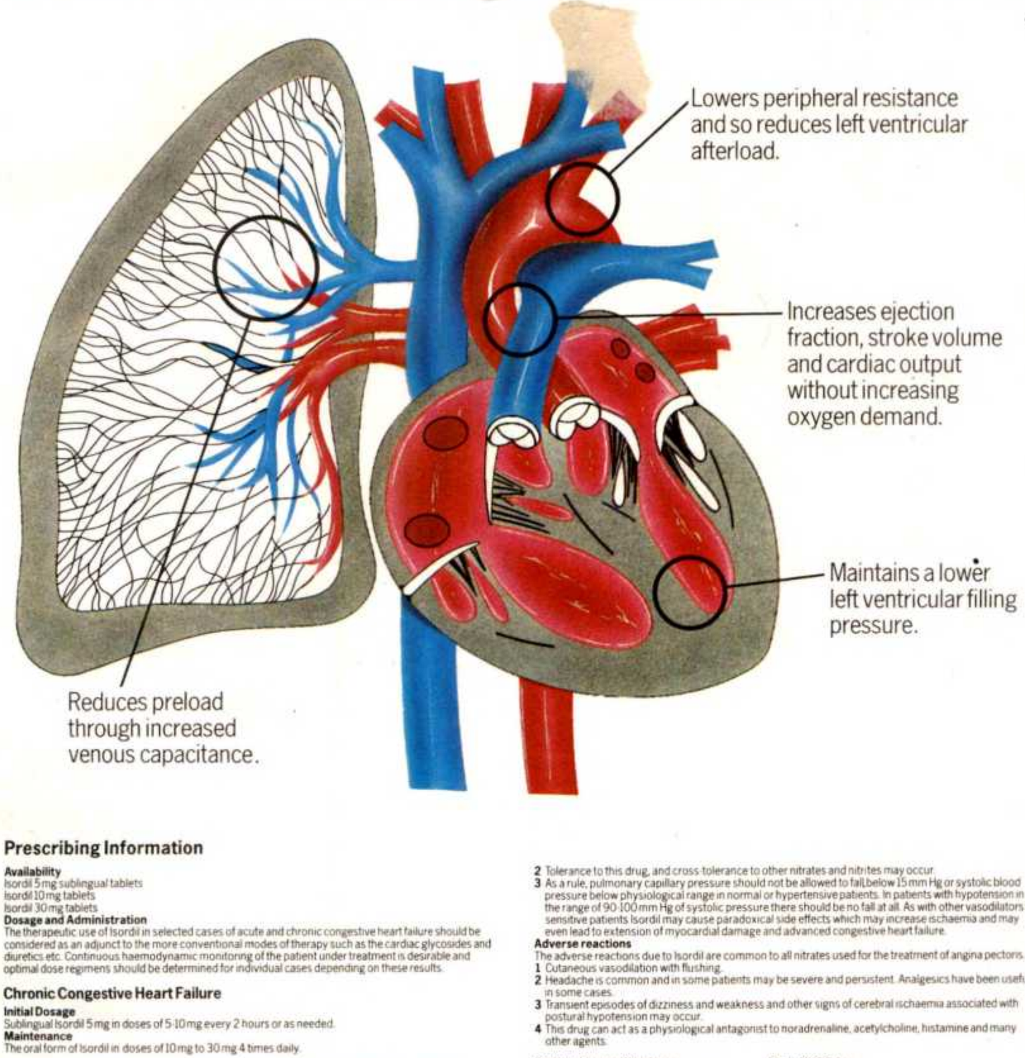

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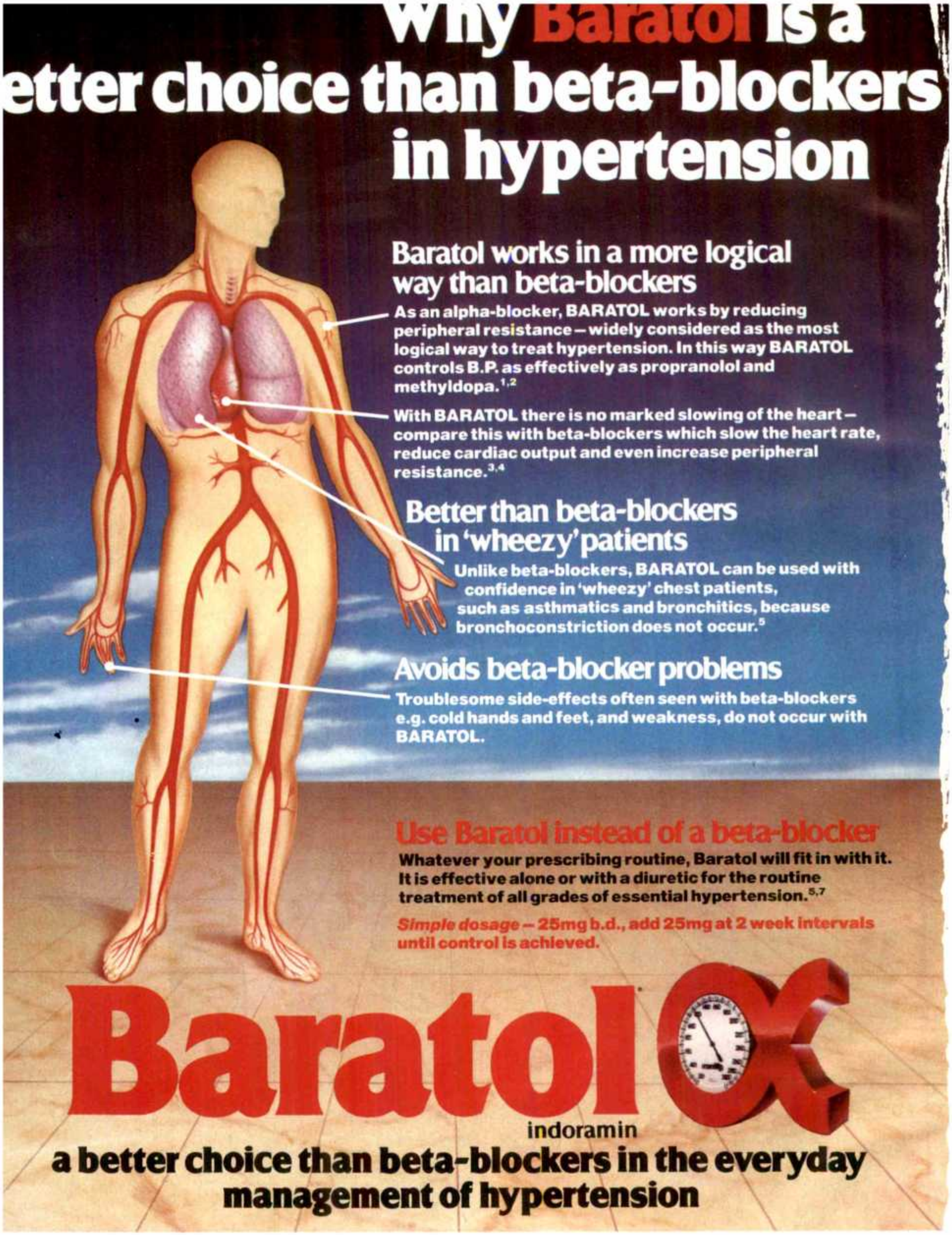

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Br Heart J 1982; **48**: 1–18

The frontiers of cardiomyopathy

JOHN F GOODWIN

From the Division of Cardiovascular Disease (Clinical Cardiology), Royal Postgraduate Medical School, and Hammersmith Hospital, London

SUMMARY The history of cardiomyopathies over the past three decades is briefly surveyed and the definition of cardiomyopathy as "heart muscle disease of unknown cause" is reaffirmed. The recent slight modification of the classification based on disorders of structure and function into hypertrophic dilated (congestive) and restrictive/obliterature cardiomyopathy is underlined.

The hypothesis that hypertrophic cardiomyopathy results from abnormal catecholamine function in the developing heart is reviewed and supported. The concept of "obstruction" in hypertrophic cardiomyopathy is critically reviewed and challenged on the basis that true obstruction to outflow from the left ventricle is not present and that the pressure gradients often recorded are the result of elimination of the cavity of the ventricle as a result of powerful contraction of extensively hypertrophied muscle. The importance of impaired diastolic function with general and regional abnormalities of relaxation of a very complex nature is stressed. The natural history of hypertrophic cardiomyopathy is reviewed and the high incidence of sudden death confirmed in a personal series of over 250 patients studied over two decades. A relation between ventricular arrhythmia and sudden death has been noted. Studies of antiarrhythmic therapy disclosed that, while neither beta adrenergic blocking agents nor calcium blocking agents such as verapamil control arrhythmias studied by ambulatory tape monitoring, amiodarone is highly effective. It remains to be seen whether amiodarone will reduce the incidence of sudden death, the mechanism of which is discussed in the light of causes other than arrhythmia such as impairment of ventricular filling and reduction in left ventricular volume. A tentative scheme of treatment is suggested based on control of symptoms with beta adrenergic blocking agents and management of arrhythmias with amiodarone. The aetiologies of dilated congestive cardiomyopathy remain obscure. The possible place of virus infection leading to a disorder of cellular immunity is stressed.

Endomyocardial fibrosis as the leading cause of restrictive/obliterative cardiomyopathy is briefly described and the similarities in pathology and haemodynamics between endomyocardial fibrosis of the tropics and Loeffler's eosinophilic endomyocardial fibrosis are stressed. Evidence that the immature eosinophils found in patients with hypereosinophilic syndrome and endomyocardial disease can damage the endocardium is reviewed.

Finally, the involvement of cardiomyopathies in many fields of general internal medicine is stressed and it is suggested that no longer are the cardiomyopathies rare or curious diseases but relatively common disorders which are of interest to medical scientists in many fields and no longer the sole problem of the cardiologist.

Historical aspects

Three decades ago the frontiers of cardiomyopathy were ill defined and nebulous because no working definition or classification had been suggested and delineation was imprecise. The cardiomyopathies were often confused with myocarditis, a term used widely in a variety of pathological and clinical contexts without clarity of expression: myocarditis was sometimes equated with cardiomyopathy, sometimes with a specific inflammatory disorder.[1] In the United States of America, Mattingly, Burch, and Proctor Harvey were selecting and studying cases in the 1950's while in 1957 Brigden published his St Cyres

Based on the Lumleian Lecture delivered at the Royal College of Physicians of London, on 10 November 1980.

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lecture on "uncommon myocardial diseases; the non coronary cardiomyopathies".[2] Brigden pointed out the diversity of the disorder and the difficulty of classification and was among the first to use the term "cardiomyopathy". Not surprisingly he regarded the cardiomyopathies as rare disorders which indeed they seemed to be at that time.

My interest was kindled by Brigden's approach and in 1961 with colleagues Gordon, Hollman, and Bishop our first paper was published defining cardiomyopathy and attempting a classification.[3] The definition was clumsy but was slightly modified in a subsequent paper on cardiac function in primary myocardial disorders as follows: "cardiomyopathy: an acute, subacute or chronic disorder of heart muscle of unknown or obscure aetiology, often with associated endocardial or sometimes with pericardial involvement but not atherosclerotic in origin".[4] At this time it was suggested that the term "primary myocardial disorder" should be used to describe those cardiomyopathies that were not the result of diseases in other parts of the heart, or elsewhere in the body; subsequently, in conjunction with Dr Celia Oakley, the definition of cardiomyopathy was simplified to "a disorder of cardiac muscle of unknown cause" while myocardial disorders that were part of a general systemic disease were termed "rare specific heart muscle diseases".[5] Thus automatically any condition of which the cause or pathological process could be defined clearly was excluded from the definition of cardiomyopathy. This concept has not always been readily accepted but has received approval from the joint task force of the World Health Organisation and International Society and Federation of Cardiology on the definition and classification of cardiomyopathies.[6]

The concept of a classification based upon the disorders of structure and function was introduced in 1964[4] when it was suggested that cardiomyopathies might present clinically in one of three ways; as congestive, constrictive, or obstructive types, respectively.

Subsequent work has shown that these types are distinct entities that do not merge from one into the other. It has also been recognised that the "obstructive" type is notable mainly for massive ventricular hypertrophy and impaired diastolic function. The definition was revised to "hypertrophic obstructive cardiomyopathy"[7] when it was realised that massive hypertrophy was a cardinal feature of the disease. At this time it was generally agreed that obstruction to outflow of the left ventricle was an important feature of the condition, though it had been recognised that in some patients no such obstruction existed. The importance of obstruction was first questioned by Criley *et al.* in 1965[8] and by our group in 1971. We noted that as the disease became more severe the signs of obstruction tended to disappear.[9] Since then, the evidence for true obstruction has become significantly less.

In addition to the hypertrophic, congestive, and constrictive types, a new group was introduced, that of obliterative cardiomyopathy, to indicate the effects of endomyocardial fibrosis in obliterating the cavity of the ventricle.[10 11]

Recently, three further changes have been made in the classification in the light of increasing knowledge. First, the word "obstructive" has been omitted from the definition of hypertrophic obstructive cardiomyopathy, and this type has come to be known simply as hypertrophic cardiomyopathy.[12-14] Second, the importance of ventricular dilatation in congestive cardiomyopathy has been recognised by the use of the word "dilated" in the definition. The term "congestive", which was introduced in 1961[3] at a time when diagnosis was seldom made before the development of florid congestive heart failure, is now felt to be inappropriate, especially as cases can now be recognised before overt congestive failure has occurred. Nevertheless, it is useful to retain the word "congestive" because it has become authenticated by frequent usage and its omission could cause confusion.

Third, the restrictive and obliterative types have been combined into one group (restrictive/obliterative) because it is known that the obliteration is merely a late stage of the restrictive type (when resulting from endomyocardial fibrosis) and a separate obliterative group is therefore not warranted[6] (Fig. 1).

It is important to emphasise the terminology used. *Elimination* refers to disappearance of the ventricular cavity by compression and apposition of its walls. *Obstruction* refers to organic mechanical hindrance to ventricular outflow. *Resistance to filling* refers to hindrance to ventricular filling caused by a stiff, irregularly relaxing, poorly compliant, hypertrophied ventricle. *Restriction to filling* refers to organic interference resulting from endomyocardial disease of the ventricle with endocardial fibrosis and thrombosis.

Despite the modifications inseparable from the growth of understanding, the classification of the cardiomyopathies has basically stood the test of time over two decades. Since any classification is necessarily incomplete and acts as a bridge between complete ignorance and total understanding in any biological system, further modification and changes are likely to occur as knowledge advances over the next two decades, and new discussions may widen the frontiers of cardiomyopathy further.

Fig. 1 shows the major characteristics of hypertrophic, congestive (dilated), and restrictive/obliterative types.

In the hypertrophic type, which is familial, there is

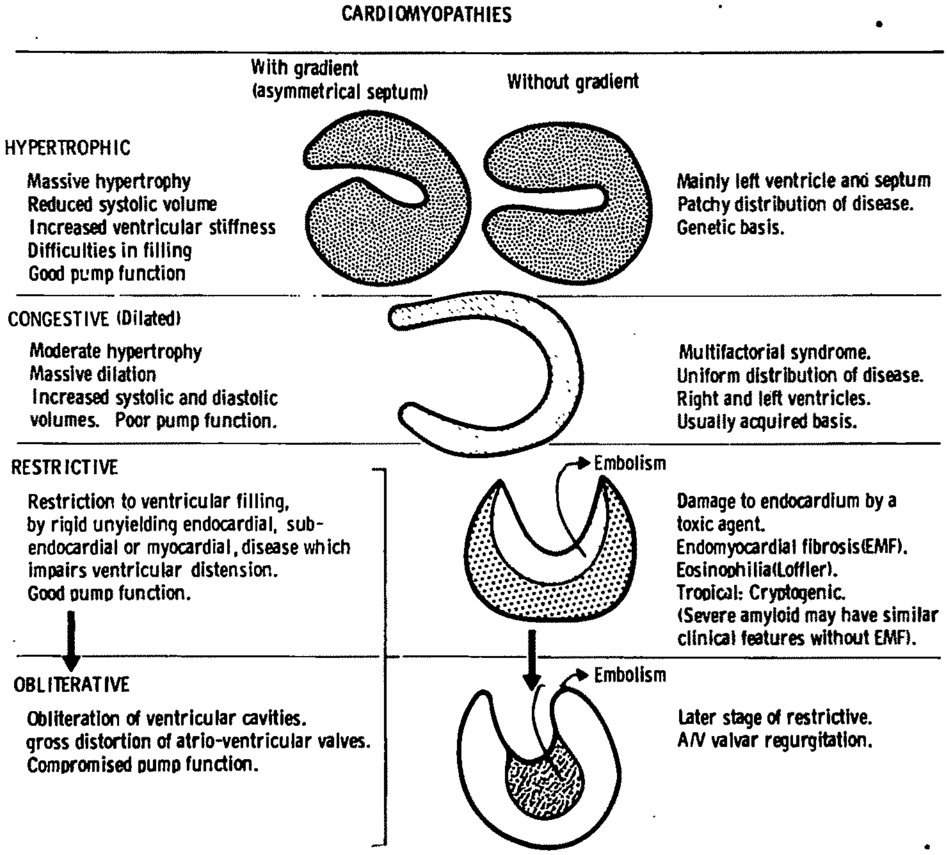

CARDIOMYOPATHIES
With gradient (asymmetrical septum)
Without gradient
HYPERTROPHIC
Massive hypertrophy
Reduced systolic volume
Increased ventricular stiffness
Difficulties in filling
Good pump function
Mainly left ventricle and septum
Patchy distribution of disease.
Genetic basis.
CONGESTIVE (Dilated)
Moderate hypertrophy
Massive dilation
Increased systolic and diastolic volumes. Poor pump function.
Multifactorial syndrome.
Uniform distribution of disease.
Right and left ventricles.
Usually acquired basis.
RESTRICTIVE
Restriction to ventricular filling, by rigid unyielding endocardial, subendocardial or myocardial, disease which impairs ventricular distension.
Good pump function.
Embolism
Damage to endocardium by a toxic agent.
Endomyocardial fibrosis(EMF).
Eosinophilia(Loffler).
Tropical: Cryptogenic.
(Severe amyloid may have similar clinical features without EMF).
OBLITERATIVE
Obliteration of ventricular cavities.
gross distortion of atrio-ventricular valves.
Compromised pump function.
Embolism
Later stage of restrictive.
A/V valvar regurgitation.

Fig. 1 *Types of cardiomyopathy. (Modified from* The heart. *4th ed. J W Hurst, R B Logue, R C Schlant, N K Wenger, editors. McGraw-Hill, New York. By permission of the editors and publishers.)*

massive muscle hypertrophy, concentration of hypertrophy in the septum, powerful systolic function, but abnormal relaxation. I now believe that obstruction in hypertrophic cardiomyopathy does not occur in a true haemodynamic and mechanical sense though gradients do develop and are important.

By contrast, the congestive dilated type has dilatation of the ventricular cavities and very poor pump function as its major characteristics. It is manifest by heart failure of unknown origin. It is now known that restrictive and obliterative cardiomyopathies are different stages of the same disease, restrictive cardiomyopathy usually being caused by endomyocardial fibrosis either of the tropical variety or of the temperate zone variety with eosinophilia, as described by Loeffler in 1936.[15]

It is the objective of this paper to indicate the direction of new advances and knowledge and to show how cardiomyopathies extend into the realms of many branches of medicine. No attempt will be made to be comprehensive or exhaustive but rather to be stimulating and provocative.

Indeterminate diseases

There are other disorders that cannot easily be classified but perhaps may be regarded as cardiomyopathy. These are: the arrhythmic syndrome in which heart failure may be produced by multiple repetitive arrhythmias which, if relieved, can be followed by improvement in heart failure; various disorders localised to the conducting tissue; prolapsing mitral valve syndrome; the long QT syndrome; and angina with "normal" coronary artries. It is not known whether this last syndrome is the result of a primary metabolic disorder or of a vascular problem but there are undoubtedly many subsets within this definition, in some of which the chest pain is not cardiac in origin.

Hypertrophic cardiomyopathy

The causation of hypertrophic cardiomyopathy is unknown but there are various clues which suggest that there may be a link between catecholamines, endocrine disorders, and hypertrophic cardiomyopathy. Experimental data show that the administration of nerve growth factor can cause hypertrophy, gradients, and myocardial fibre disarray in dogs, which also have an increased amount of catecholamines in the base of the heart. The condition so produced is irreversible. Witzke and Kaye[16] suggested that there might be abnormal receptors in the heart. Laks *et al.*[17] and Blaufuss *et al.*[18] have shown that noradrenaline in subhypertensive doses causes hypertrophic cardiomyopathy in dogs. In the clinical field adrenergic stimulation increases gradients and reduces diastolic compliance in the left ventricle, while beta adrenergic blockade reverses these effects.[19] There is an association between disorders of catecholamines and neural crest tissue, such as neurofibromatosis, phaeochromocytoma, and lentiginosis.[20–22] Friedreich's ataxia[23, 24] is also associated with a hypertrophic type of cardiomyopathy and some evidence of autonomic disorder.[23, 24] In addition, systemic hypertension is present in around 10% of patients with hypertrophic cardiomyopathy. The finding of extensive noradrenosis in the outflow tract of the left ventricle in hypertrophic cardiomyopathy by Everson Pearse[25] has not been confirmed.

There is additional evidence of an endocrine character. Reversible hypertrophic cardiomyopathy has been noted in the infants of diabetic mothers.[26] Triiodothyroacetic acid (TRIAC) given to pregnant rats caused myofibrillar disarray in the heart of the fetus but not of the mother.[27] There is an association between hyperthyroidism and hypertrophic cardiomyopathy.[28, 29] Hyperinsulinism and hypoglycaemia may be associated with hypertrophic cardiomyopathy and increased catecholamine excretion. Experimental fetal hyperinsulinism causes selective organ enlargement including the heart and it has been suggested there may be insulin receptors in the heart.[30] Hyperinsulinism and cardiac hypertrophy occur in the Leprechaun syndrome.[31] A relation between hypercalcaemia and catecholamines has been proposed by McFarland *et al.*[32]

I have, therefore, speculated whether hypertrophic cardiomyopathy may be a genetically determined disorder of handling of catecholamines by the developing fetal heart.[1, 11] Ferrans *et al.*[33] noted the similarity of the abnormal myofibrillar arrangements to the normal appearances in primitive hearts such as the salamander, while Manasek[34] had previously noted that the normal myofibrillar alignment depends on the stresses of contraction and relaxation of the developing heart. Abnormal alignment resulting from developmental error might affect relaxation and contraction.

Perloff[35] has summarised the evidence for the pathogenesis of hypertrophic cardiomyopathy based on this catecholamine hypothesis. He agreed that hypertrophic cardiomyopathy might well have its origin in utero. This would harmonise with my suggestions[1, 11] that hypertrophic cardiomyopathy might be the result of abnormal responses of developing heart muscle to circulating catecholamines. Perloff added the interesting suggestion that there may be a failure of the normal regression of disproportionate septal thickness and myocardial fibre disarray in fetal life because of faulty interaction between noradrenaline and myocardial receptor sites.

Work on catecholamines and hypertrophic cardiomyopathy in man has been scanty but Dargie *et al.* (to be published) at the Royal Postgraduate Medical School have shown that plasma noradrenaline increased in the lying and standing positions during the cold pressor test and isometric handgrip, as compared with controls (Fig. 2). But these studies of peripheral catecholamine levels give little idea of cardiac catecholamine status. Further work is planned to investigate the catecholamine function of the heart.

Table 1 *Causes of sudden death in hypertrophic cardiomyopathy*

Cause	*Mechanism*	*Reason*	*Frequency*	*Prevention*
(1) Arrhythmia	(a) Ventricular tachycardia (increased automaticity; local re-entry)	Myofibrillar disarray and fibrosis	Common	Amiodarone
	(b) Pre-excitation	Abnormal connections between atrium and ventricle bypassing A/V node	Rare	Amiodarone
(2) Haemodynamic	Reduction in left ventricular volume with apposition of ventricular wall and septum and loss of effective output (gradients variable); violent contraction of hypertrophic left ventricle	Resistance to filling of stiff incompliant left ventricle; tachycardia limiting time available for filling; loss of atrial contraction; powerful rapid contraction of left ventricle	Uncertain	Avoid: vasodilatation; hypotension; hypovolaemia and avoid: undue tachycardia (SR or AF); positive inotropic drugs unless AF demands digitalis

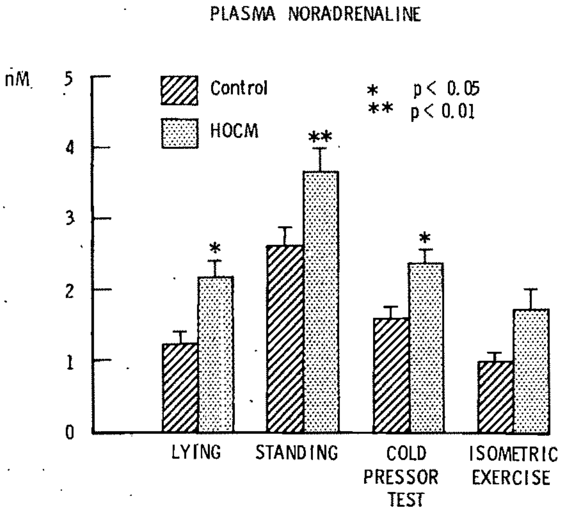


Fig. 2 *Plasma noradrenaline levels in patients with hypertrophic cardiomyopathy (HOCM) and in control subjects in lying and standing positions and after isometric handgrip and cold pressor stimulation. There is a significant increase in catecholamine levels in the cardiomyopathy patients. (Reproduced by permission of Dr Henry Dargie.)*

WHAT IS OBSTRUCTION?

I have stated[14] that true obstruction is a myth. It has been assumed, and is still accepted in many quarters, that true obstruction of blood flow from the left ventricle is an important feature of hypertrophic cardiomyopathy. It is true that pressure gradients in systole are commonly, though not invariably, present and that they are of importance. They do not, however, constitute genuine haemodynamic obstruction to outflow in the accepted sense as, for example, occurs in severe valvar aortic stenosis. The variability of the gradient; the lack of correlation between gradients and prognosis, symptoms, or progression of the disease; the discharge of all the contents of the left ventricle in the first half of systole and the tendency for gradients to disappear as the disease advances,[9] together with a tendency for more widespread ventricular involvement to be unassociated with a gradient[33 36] all support this contention. Furthermore, gradients can be produced in any heart by powerful inotropic stimulation or acute ventricular hypovolaemia.[8] These views are supported by the elegant work of Murgo *et al.*[37] who measured high velocity flow and pressure in the left ventricle and aorta. These workers were unable to show any evidence of true obstruction to outflow from the left ventricle. Ejection was completed earlier than in normal subjects and was independent of gradients. They concluded that hypertrophy and abnormal ventricular compliance play the dominant roles in hypertrophic cardiomyopathy.

Angiocardiography shows almost complete or complete elimination of the apex and body of the left ventricle in systole in many cases and demonstrates the apposition of the mitral valve to the septum caused by the powerful contraction and the reduction in ventricular volume. The abnormal angulated shape of the left ventricle with massive papillary muscles of the mitral valve and massive hypertrophy of the septum and free wall is associated with greatly reduced left ventricular volume in systole (Fig. 3). The cavity is virtually squeezed out of existence by the fierce contractile action of the increased muscle mass. Indeed the cavity of the left ventricle is neither *obstructed* nor *obliterated*, but rather is virtually *eliminated*.

Systolic anterior movement of the mitral valve apparatus and mid-systolic closure of the aortic valve are present when gradients are found.[38] It is the papillary muscles rather than the cusp of the mitral valve, however, that meet the hypertrophied septum.[39] The apex of the left ventricle is eliminated by the powerfully contracting hypertrophied muscle mass (Fig. 4, Fig. 5).

Gradients, however, are important and should not be dismissed. They are diagnostically valuable; they warn that powerful inotropic agents, manoeuvres, or drugs that reduce ventricular volume can be dangerous; the presence of persistent gradients warns of possible associated fixed outflow tract obstruction requiring operation; and finally septal resection in selected patients can produce symptomatic relief though it does not improve prognosis.

I do not support the view of Gilbert *et al.*[40] that there are two types of patients with hypertrophic cardiomyopathy: those with obstruction (persistent or latent) and those without, with significant differences in function and prognosis. The presence or absence of gradients appears to be largely coincidental and not an indication of the basic and important underlying abnormalities of the disease.

DIASTOLIC FAULTS

The work of Webb Peploe *et al.*[19] in our laboratory and later at St Thomas's Hospital[41] showed that beta adrenergic blocking agents administered acutely produced an increase in left ventricular volume and a fall in left ventricular diastolic pressure, suggesting an improvement in diastolic function. It was suggested[11] that catecholamine stimulation produced a fall in volume with an increase in diastolic pressure and beta blockade produced the reverse.

The rates of filling and relaxation of the left ventricle were studied by our group in collaboration with Dr Derek Gibson of the Brompton Hospital. Using angiocardiographic[42] and echocardiographic techni-

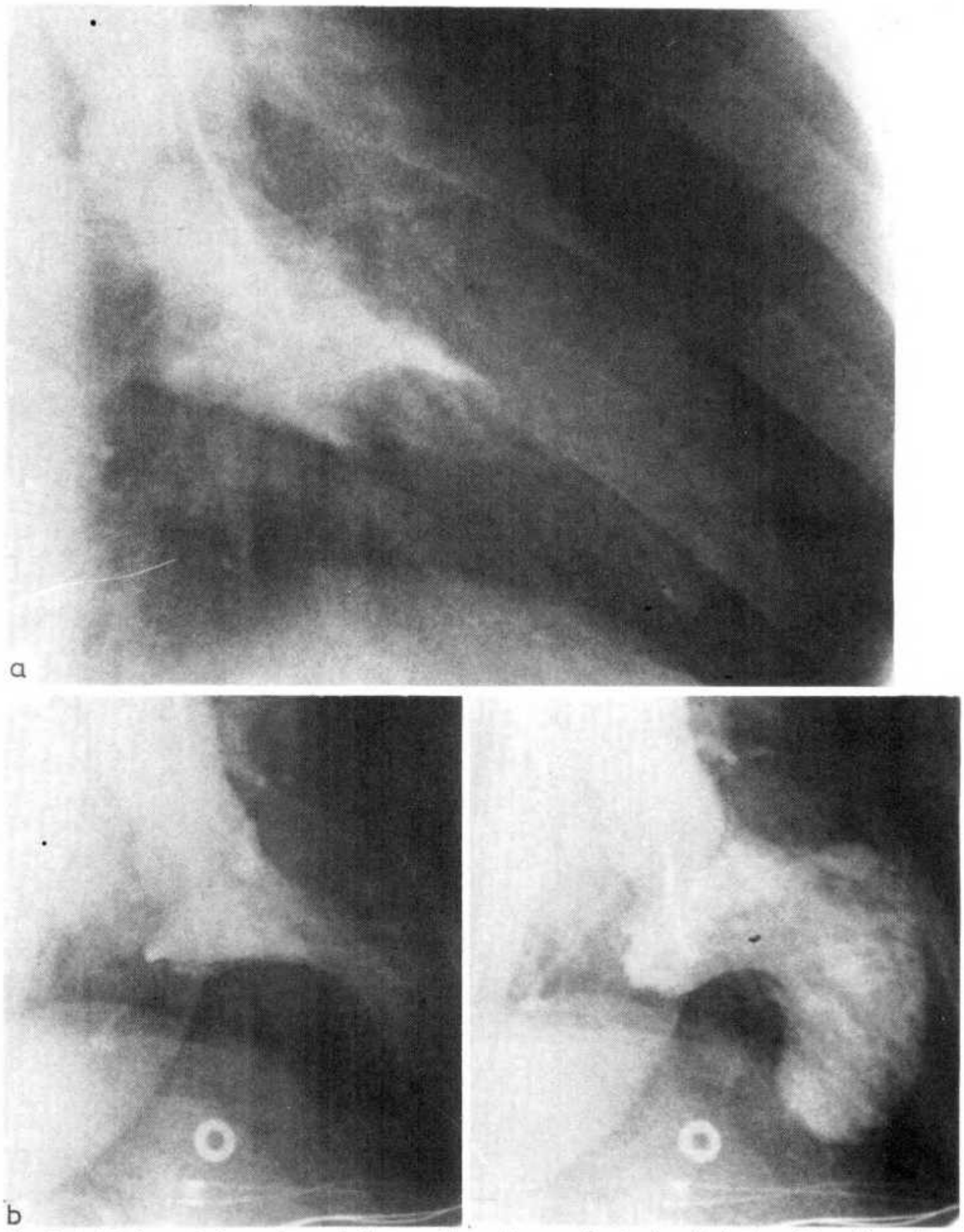


Fig. 3 *(a) Left ventricular angiogram in hypertrophic cardiomyopathy showing elimination of the mid-portion and apex of the left ventricular cavity. (b) Left ventricular angiogram in hypertrophic cardiomyopathy showing angulation of left ventricular cavity. Left: systolic frame. Right: diastolic frame.*

ques[43] we showed delay in opening of the mitral valve, indicating abnormal relaxation. Peak filling rate of the left ventricle correlated inversely with this delay. Isovolumic relaxation time was prolonged and this was considered to be a primary abnormality in hypertrophic cardiomyopathy. End-systolic dimensions were reduced and the rapid filling period tended to be prolonged. The filling pattern was abnormal, due both to impaired relaxation and to abnormal shape of the left ventricular cavity. Previous work by

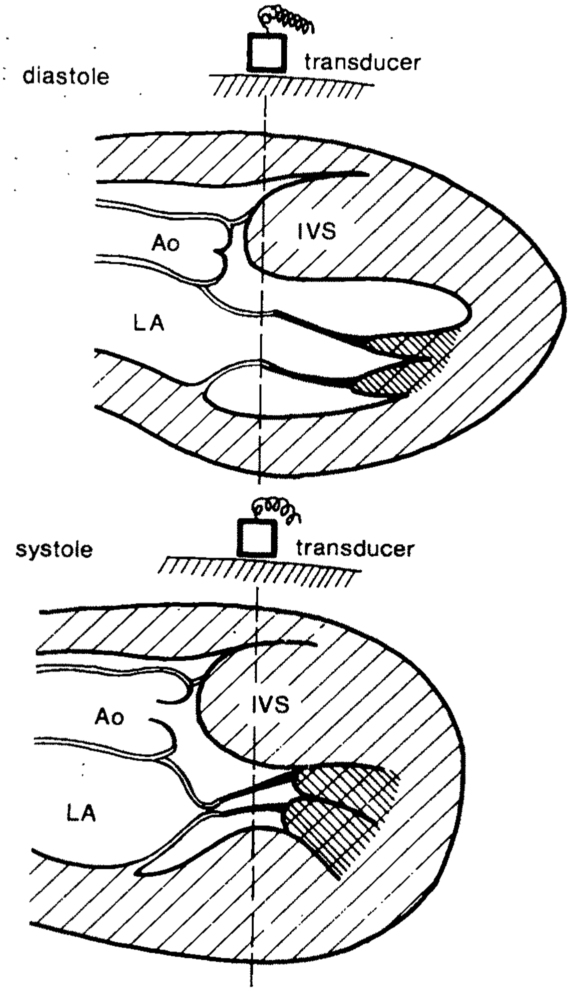


Fig. 4 *Diagrammatic representation of the left ventricle, papillary muscles, chordae, and cusps of the mitral valve in diastole (top) and systole (bottom), as viewed from the transducer of the echocardiograph. The contraction of the hypertrophic ventricular muscle forces the chordae and papillary muscles against the septum, eliminating the cavity. (Reproduced from Gehrke J and Goodwin J F* Clinical Cardiology *1978;* 1: *152–72, with permission of the authors and editors of* Clinical Cardiology.)

Upton and colleages[44] had shown that left ventricular wall movement was incoordinate, patchy, and not uniform.

Hanrath *et al.*[45] also reported prolonged isovolumic relaxation and a reduction in the rapid filling phase of diastole with an increase in ventricular dimensions.

Alvares[46] in our laboratory using phonocardiography, apex cardiography, and M-mode echocardiography showed that the normal sequence of events in diastole is completely disrupted in hypertrophic cardiomyopathy. Aortic valve closure occurred after the minimum dimension of the left ventricular cavity, and the isovolumic relaxation period (from aortic valve closure to mitral valve opening), though often prolonged, tended to be shortened in patients with gradients (Fig. 6). The effects of chronic beta adrenergic blockade were variable. In the majority of patients the active suction period was prolonged, thus aiding ventricular filling, but in the minority was shortened (Fig. 7). These results indicate the variability and incoordination of ventricular diastolic function and thus the difficulty of predicting the effects of any particular drug. They also explain the diverse effects of beta adrenergic blockade.

It is apparent that the diastolic abnormalities in hypertrophic cardiomyopathy are the most important feature of the disease and are exceedingly complex. Far from being uniform, they are patchy and irregular, depending upon the extent and distribution of the myofibrillar lesions. Generalisations as to the exact disorder of the normal filling pattern in any individual patient are likely to be fallacious.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY

When gradients are present the diagnosis can be made at the bedside by three cardinal physical signs. The *ejection murmur* of late onset is heard at the apex, at the left sternal edge, and occasionally at the base of the heart. The *arterial pulse* shows a rapid upstroke and rapid decline and has an ill-sustained or jerky quality. The third sign is the *palpable atrial beat* caused by the strong contraction of the left atrium needed to fill the stiff left ventricle (Fig. 8).

When gradients are present the differential diagnosis must include aortic valvar stenosis, subvalvar stenosis, mitral regurgitation, and ventricular septal defect but when the three major physical signs are present and when there is a family history of sudden death and symptoms of angina, dyspnoea, and syncope a diagnosis of hypertrophic cardiomyopathy can be made reliably at the bedside.

When gradients are absent and there is little if any murmur the diagnosis is much more difficult. The heart may even appear to be normal, though a palpable left atrial beat and jerky pulse are useful clues. Sometimes pulmonary hypertension may be noted because of the high left ventricular end-diastolic pressure.

When there is an apical mid-diastolic murmur, mitral valve disease or left atrial myxoma may be suggested, while when there is mitral valve calcification and atrial fibrillation the differentiation from rheumatic heart disease can often not be made clinically and depends upon angiocardiography. In patients with

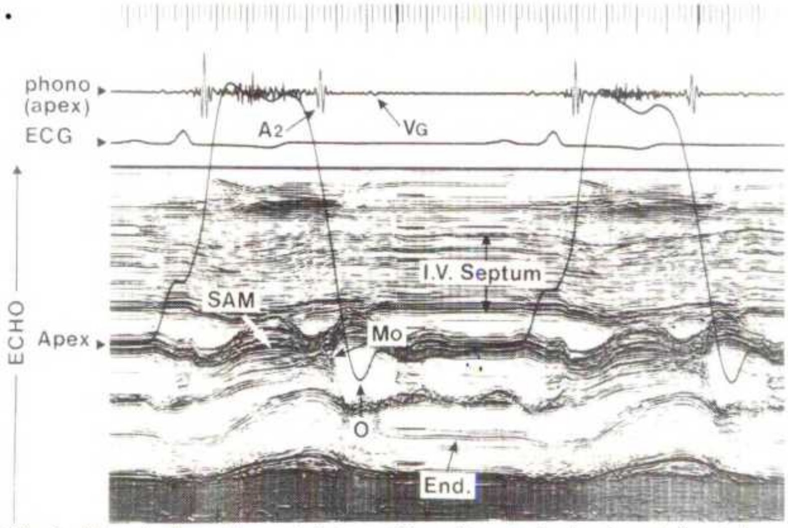


Fig. 5 *M-mode echocardiogram in hypertrophic cardiomyopathy showing systolic anterior movement of the mitral valve. The slit-like cavity of the left ventricle is almost eliminated in systole by the hypertrophied ventricular muscle and the mitral valve apparatus. The mitral valve cusps are thickened, probably as a result of turbulence of blood flow. (Courtesy of R Alvares, PhD.)*

angina but no abnormal physical signs, electrocardiography showing deep T wave inversion, left atrial enlargement, and Q waves may suggest the diagnosis.

It is probable that hypertrophic cardiomyopathy masquerades as other conditions more frequently than is generally realised.

MOST IMPORTANT DIAGNOSTIC TEST

M-mode echocardiography is of value when all the features are present, namely disproportionate septal thickness, apparently poor movement of the septum, reduced systolic diameter of the left ventricle, prolonged diastolic closure rate of the mitral valve, systolic anterior movement of the mitral apparatus, and mid-systolic closure of the aortic valve. But these features can be found singly or even in combination in other conditions.

M-mode echocardiography may fail to show any features of hypertrophic cardiomyopathy in a proven case. This is particularly likely to be the case where septal hypertrophy is localised and particularly asymmetrical and disproportionate.

In my experience the most important diagnostic test is the angiocardiogram (Fig. 3). A detailed analysis of 100 of our patients showed that 90 had either *elimination* of the left ventricular cavity or pronounced narrowing of the mid portion of the ventricle, with angulation of the body. Sometimes contrast medium may be squeezed into the apex and almost isolated from the main cavity (Fig. 9). In six patients the cavity appeared normal or the papillary muscles merely somewhat prominent. In four patients the cavity was dilated. Characteristic features thus occur in 90% of patients but the disease can exist with almost normal appearances. *Dilatation* of the left ventricle is very rare and when it occurs is likely to be associated with severe widespread disease, extreme mitral regurgitation, or massive myocardial infarction.[47] Ventricular dilatation does not indicate that hypertrophic cardiomyopathy has progressed to dilated congestive cardiomyopathy, which is an entirely different disease.

EXPERIENCE IN PROGNOSIS: INCIDENCE OF SUDDEN DEATH

My colleagues and I now have experience of 254 patients followed for up to 23 years with a mean of six years. Forty-eight patients died, 32 of them suddenly. The deaths in other patients were mainly the result of congestive heart failure; embolism or infective endocarditis were uncommon causes.[48] The high incidence of sudden death has been noted by many investigators and was also seen in our previous studies.[49] Of 119 patients, 69 with a gradient, 30 died, 19 suddenly. In the multicentre study of Shah *et al.*,[50] in which we took part, of 190 patients, 49 died, 26 suddenly. No definite features predictive of sudden death could be detected at that time, but we now consider that young age (14 years or less), a strong family history, and progressive symptoms are all fea-

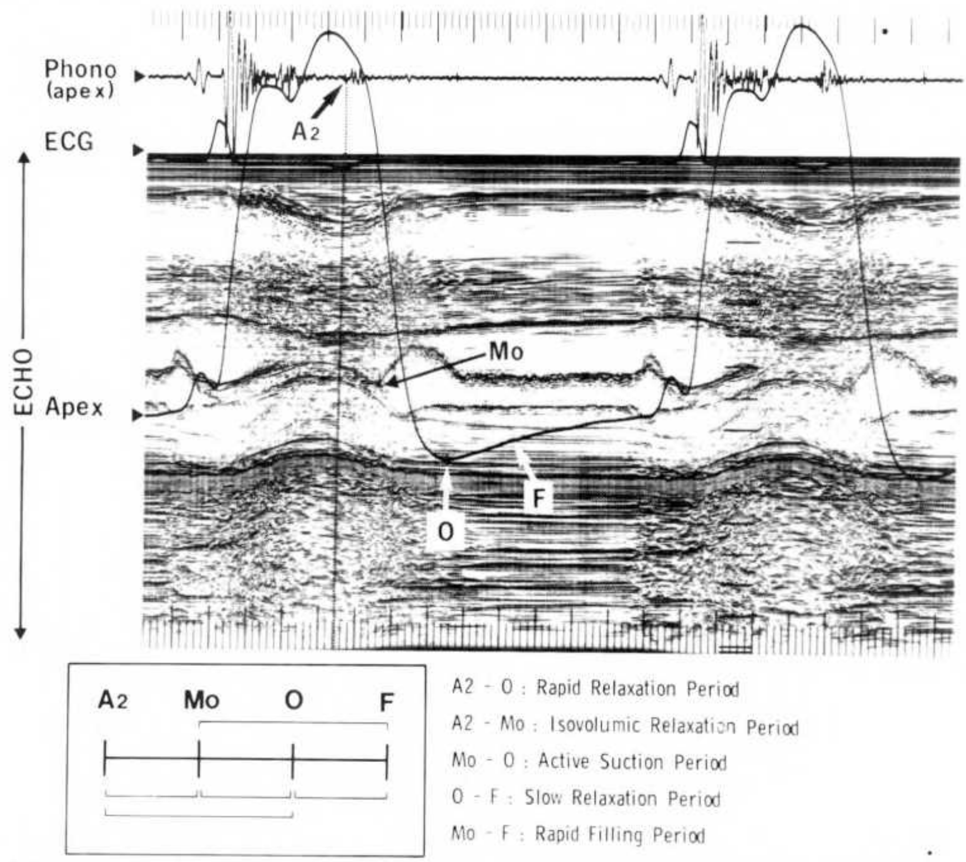

Phono (apex)
ECG
A2
ECHO
Apex
Mo
F
O
A2
Mo
O
F
A2 - O : Rapid Relaxation Period
A2 - Mo : Isovolumic Relaxation Period
Mo - O : Active Suction Period
O - F : Slow Relaxation Period
Mo - F : Rapid Filling Period

Fig. 6 *Diastolic time intervals in hypertrophic cardiomyopathy. Aortic valve closure (A2) occurs after the minimum dimension of the left ventricular cavity (Mo, mitral valve opening; O, nadir of apex cardiogram trace; F, end of slow relaxation period, SRP). (See text.) (Reproduced from Alvares R, PhD Thesis, University of London 1980, by permission of the author.)*

tures suggesting a bad prognosis. The history, and particularly changes in symptoms, appear to be better predictors of poor prognosis than any haemodynamic or electrocardiographic measurements. Maron *et al.*[51] described families of "malignant" hypertrophic cardiomyopathy with a high incidence of sudden death.

Although sudden death was originally thought to be caused by outflow tract obstruction, attention has recently been given to the possibility of arrhythmia as a cause by Goodwin and Krikler[52] and by Maron *et al.*[53] Krikler *et al.*[54] described two patients who died suddenly. One patient had documented ventricular fibrillation, the other had both a short PR interval and wide QRS complex, while there was a family history of sudden death in both. At necropsy accessory bypass tracts were seen between the atrium and ventricle on the right side of the septum. Ingham *et al.*[55] described 13 patients with arrhythmias and conduction defects. Electrophysiological studies showed prolonged His-Purkinje conduction. It is probable, however, that ventricular arrhythmias are a more frequent cause of sudden death than supraventricular and that true pre-excitation is unusual in hypertrophic cardiomyopathy. Savage *et al.*[56] noted ventricular arrhythmias in 50 of 100 patients subjected to ambulatory electrocardiographic monitoring and effort testing.

A relation between sudden death and ventricular arrhythmia has been established by our group.[57] This study examined the incidence of ventricular tachycardia and sudden death in a 72 hour electrocardiographic monitoring study of 86 patients. During monitoring 23 patients had ventricular tachycardia, 10 having more than three episodes. The patients were followed for between one to four years (mean 2·6 years). Seven died suddenly, and, of these, five had either multiform paired premature ventricular contractions or episodes of ventricular tachycardia. Ven-

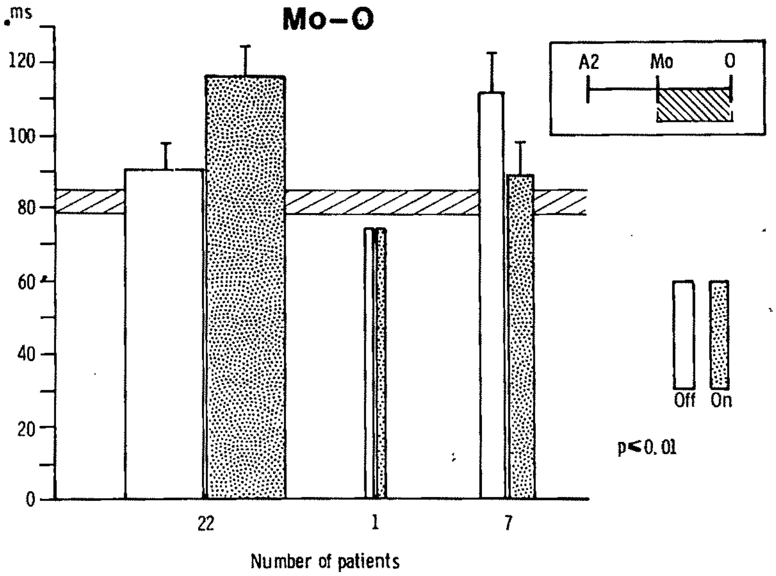


Fig. 7 *Effects of long term beta adrenergic blockade on diastolic time intervals in hypertrophic cardiomyopathy. The active suction period from opening of the mitral valve to the nadir of the apex cardiogram (Mo—O is prolonged in most, but not all, patients on beta blockade (hatched columns). (Reproduced from R Alvares, PhD Thesis, University of London, 1980, by permission of the author.)*

tricular tachycardia was significantly associated with sudden death in older patients who had symptoms. This may or may not be true of younger patients also. There was no significant relation between supraventricular tachycardia and sudden death.

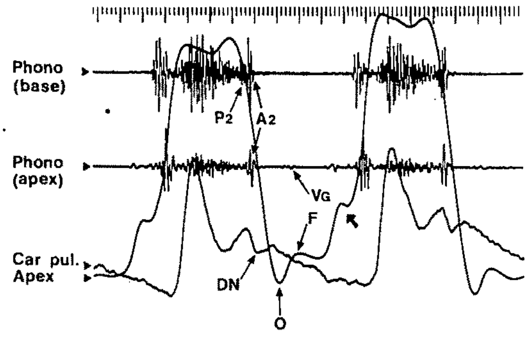


Fig. 8 *Phonocardiogram, carotid pulse tracing, apex cardiogram, electrocardiogram in hypertrophic cardiomyopathy showing the ejection murmur starting after the first heart sound, delayed aortic valve closure (P2, A2), sharply rising ill-sustained arterial pulse, atrial beat (thick arrow), and third heart sound (VG). (Reproduced from R Alvares, PhD Thesis, University of London, 1980, by permission of the author.)*

EFFECT OF DRUGS ON ARRHYTHMIA AND PREVENTION OF SUDDEN DEATH

The lack of effect of beta blockade in preventing sudden death has been reported.[58] In our studies[50] about 50% of patients who died suddenly were on beta adrenergic blockade. These results and those of others suggest that beta blocking agents do not prevent sudden death. Neither at rest nor on effort did beta blockade alter the incidence of supraventricular or ventricular arrhythmia. A few years ago Krikler and I theorised that the calcium blocking agent verapamil might be more effective than beta adrenergic blocking agents.[52] But our further study[59] of verapamil in an ambulatory electrocardiographic investigation showed that there was no significant reduction in the frequency of arrhythmias while on verapamil.

Amiodarone, however, abolished ventricular tachycardia in 10 of 13 patients.[59] Amiodarone represents a significant advance in the treatment of arrhythmias in hypertrophic cardiomyopathy but we do not yet know whether it has significant haemodynamic effects. It is my impression that amiodarone improves severe cardiac pain, possibly because of its beta blocking action. Arrhythmia may not always be responsible for sudden death. Another possible cause was illustrated by one of our patients, reported by McKenna *et al.*[60] This patient, while walking to the *x*-ray department with an escort, and wearing a 24 hour continuous monitor, suddenly

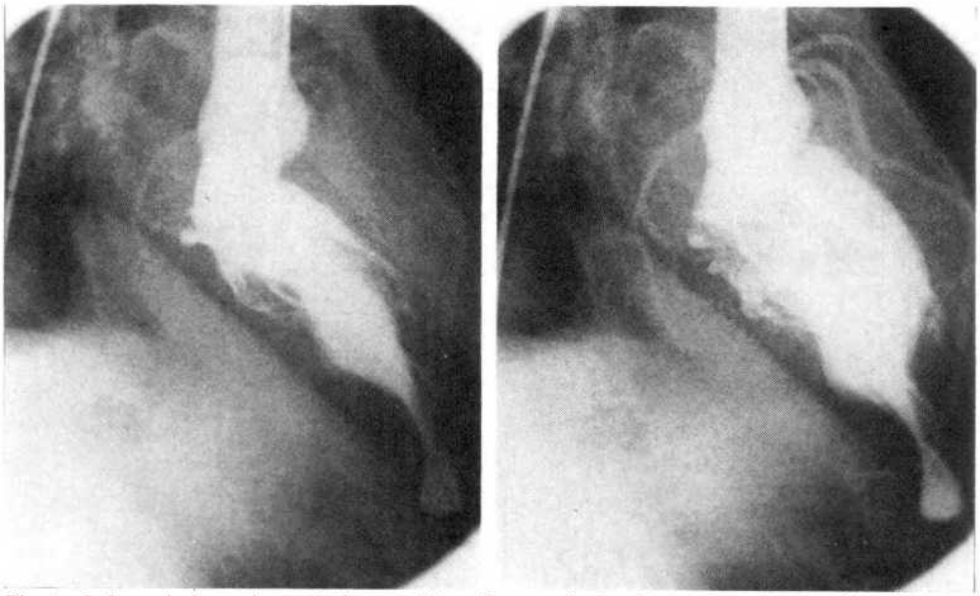


Fig. 9 *Left ventricular angiogram by hypertrophic cardiomyopathy showing extreme narrowing of the distal portion of the cavity and almost complete elimination of the apex with isolation of the tip of the ventricle from the proximal cavity. Left: systolic frame. Right: diastolic frame.*

complained of feeling faint and lost consciousness. Her pulse disappeared for over a minute before she was resuscitated. In the early stages of the attack tachycardia and ischaemic ST segment changes occurred. In the early recovery phase there was some atrioventricular dissociation and fusion beats, but no bradycardia, cardiac arrest, or ventricular tachycardia or fibrillation. Subsequent tracings during recovery also showed pronounced ST segment depression. On another occasion several episodes of ventricular tachycardia occurred of which she was quite unaware and which did not produce symptoms. Some haemodynamic event had occurred in the left ventricle to produce the syncopal attack and acute ischaemic changes. It is likely that a sudden reduction in ventricular volume was produced by peripheral vasodilatation which resulted in further reduction in filling of the left ventricle, made worse by the tachycardia.

MECHANISMS OF SUDDEN DEATH (Table 1)

These are complex and interactive. They relate both to arrhythmia and to haemodynamic changes. The haemodynamic changes are probably related to acute reduction in left ventricular volume and to resistance to filling of the left ventricle. The end-systolic volume of the left ventricle is smaller than normal and relaxation is prolonged. If the ventricle does not fill adequately, the volume will be further reduced, which will encourage apposition of the massive left ventricular wall to the septum. In this way the cavity of the left ventricle is ***eliminated*** (not obstructed) (Fig. 4). The anterior mitral valve apparatus meets the septum and this is how gradients are created. The combination of resistance to filling of the left ventricle, reduced left ventricular volume, and powerful left ventricular contraction together cause a sudden dramatic fall in effective left ventricular outflow. This is the "obstruction" so frequently discussed (Fig. 4).

It follows that measures to prevent sudden death must include antiarrhythmic drugs in patients shown to have arrhythmias by ambulatory electrocardiographic monitoring. In our experience beta adrenergic blocking agents, verapamil, and the usual antiarrhythmic drugs have not been successful. Propranolol has been disappointing, though Frank *et al.*[61] reported reduction in the incidence of death with very large doses of propranolol. But, in our hands, only amiodarone has been successful.

Systemic hypotension, hypovolaemia, and vasodilatation should be avoided, as should undue tachycardia and positive inotropic drugs and manoeuvres. Digitalis is usually better not given, the exception being the presence of rapid atrial fibrillation in which the ventricular rate must be slowed.

BETA ADRENERGIC BLOCKING AGENTS, CALCIUM AGENTS, AND ANTIARRHYTHMIC AGENTS

Treatment should aim at reducing symptoms, preventing sudden death, and retarding the advance of the disease. These different aspects and the varying patterns of the disease in different patients indicate that treatment must be adjusted to the individual. It is clear that the practice of administering propranolol or other beta blocking agents on a routine basis to all patients is now obsolete and untenable.

Before deciding on the best form of treatment the patient should have a 48 or 72 hour ambulatory electrocardiographic study. If this indicates premature ventricular extrasystoles or runs of ventricular tachycardia then amiodarone should be given in a dose of 600 mg daily for one week, and then 400 daily. If the patient also has symptoms of dyspnoea and angina these may respond to amiodarone alone. If not, propranolol or another non selective beta blocking agent should be given cautiously in addition, starting with a small dose of 10 mg four times daily and increasing carefully. We do not yet have data on the results or risks of combined treatment with amiodarone or beta blockade, so caution is necessary. But theoretically this combination is attractive as it has the twin aims of improving prognosis and relieving symptoms.

If there are no arrhythmias, but symptoms are present, propranolol should be given as the sole drug. If beta adrenergic blocking therapy is not successful, verapamil may be tried. In some patients it certainly improves symptoms, haemodynamics, and exercise capacity,[62 63] but other patients do badly, as we have noted. Hypotension and lengthening of the PR interval may occur on intravenous administration.[62 63] Rosing *et al.*[64] were obliged to discontinue oral verapamil because of sinus arrest and hypotension in one patient after a single dose of 80 mg verapamil, while another patient developed second degree intraventricular block. Two additional patients died; one developed severe chest pain after four doses of 80 mg of verapamil and the other died during operation for septal resection, having previously developed pulmonary oedema on verapamil at a dose of 130 mg six hourly for 13 doses.

The long term effects of verapamil have also been studied.[64] Of 78 patients, 54% obtained sustained symptomatic improvement over periods of from six to 30 months. Haemodynamic and electrophysiological changes occurred in 19 patients (25%). Three patients died in pulmonary oedema. Rosing *et al.* remarked that verapamil should not be given if there is evidence suggesting pulmonary venous hypertension and that treatment should not be started if the indirect left atrial pressure exceeds 22 mmHg.

Care is obviously necessary in using verapamil and it should not be the first line of treatment, but in patients who cannot tolerate or do not respond to beta adrenergic blocking agents, verapamil may be given cautiously, in doses of 20 mg three times daily, increasing gradually if no adverse effects occur, to 80 mg four times daily. Larger doses are occasionally employed, but should be used with caution. The objective of verapamil treatment should be improvement in symptoms, haemodynamics, and exercise capacity rather than relief of arrhythmia. We do not have experience of the combination of verapamil and amiodarone because this would be dangerous. Patients should be kept under close observation in hospital when starting verapamil.

Kaltenbach *et al.*[65] claimed that verapamil reduced left ventricular mass in hypertrophic cardiomyopathy and have suggested that it may be better treatment than beta blocking agents.

It is tempting to hope that propranolol might reduce left ventricular hypertrophy by diminishing the force of contraction of the left ventricle. Though the work of Vaughan Williams *et al.*[66] showing reduction of rate of growth of the myocardium in small animals given propranolol, there is no clinical evidence to indicate that this happens in man with hypertrophic cardiomyopathy.

The place of other calcium blocking agents such as nifedipine and diltiazem is not known. Nifedipine has been shown to improve diastolic function in acute haemodynamic observations.[67] Care should be taken with nifedipine because it can produce considerable vasodilatation and hypotension and could thus precipitate syncope.

SURGICAL TREATMENT

Septal resection is indicated in a small group of patients with persistent outflow tract gradients of greater than 50 mmHg, severe symptoms which do not respond to medical treatment, and pronounced septal and papillary muscle hypertrophy. The immediate results are gratifying in terms of relief of symptoms and improvement in haemodynamics but the mortality is high, and there is an incidence of late congestive heart failure after the operation.[68 69] Kuhn *et al.*,[70] however, claimed a surgical mortality half that which occurred in patients treated with propranolol.

Mitral valve replacement is indicated for severe intractable mitral regurgitation which occurs as a complication in up to 5% of cases as a result of calcification, turbulence, or infection. Resection of the mitral papillary muscles which is implicit in the operation also removes any systolic left ventricular gradients that may be present.

TREATMENT FOR ATRIAL FIBRILLATION AND CONGESTIVE HEART FAILURE

Immediate cardioversion is required if rapid atrial fibrillation develops. Heparin should be given to prevent embolism. After conversion to sinus rhythm amiodarone may.be given as it is likely to maintain the patient in sinus rhythm, or, if not, to stabilise the atrial fibrillation. Alternatively, a small dose of digitalis may be given along with a small dose of beta adrenergic blocking agent. Amiodarone may be given in conjunction with digitalis but it tends to increase the effects of digitalis on the heart so caution is necessary. Congestive heart failure implies advanced and severe widespread disease that should be treated in the usual way with diuretics which must be used with great care in patients with persistent outflow tract gradients. Vasodilator therapy for heart failure is contraindicated.

When congestive heart failure develops, gradients usually disappear,[9] but in some patients these may remain. Such patients are all too often intractable therapeutic problems; the risks of surgical treatment are very high and the results poor.

Much has been learned about hypertrophic cardiomyopathy over the past two decades. The impressions gained initially have been revised in the light of new knowledge. Clues as to prognosis are emerging and we can expect treatment to become more rational. The catecholamine theory of causation of hypertrophic cardiomyopathy, while not proven, has much theoretical, circumstantial, and some practical appeal.

Dilated congestive cardiomyopathy

This is a syndrome of dilated ventricles, gallop rhythm, and congestive heart failure, with gross impairment of systolic function. The disease usually involves both ventricles, but a right ventricular variety may occur. The cause or causes are not known. Possible associated or conditioning factors include high and prolonged intake of alcohol,[71] high blood pressure,[72] pregnancy or the puerperium, [73 74] and a disorder of cellular immunity resulting from infection.[75 76] In 1967 a new infective agent was postulated but has not been confirmed.[77]

The pathology yields no clues; the heart is dilated and overweight, but thickness of the ventricular walls is not increased. There are no valvar or coronary artery lesions and histology shows variable degrees of fibrosis. Cellular infiltration suggests a diagnosis of myocarditis. Electronmicroscopical studies show major abnormalities but none to indicate aetiology.

The diagnosis of dilated congestive cardiomyopathy is basically one of exclusion. Heart failure of unknown cause without evidence of underlying heart disease or disease elsewhere in the body sums up the usual presentation. Some patients, however, may be detected before overt congestive heart failure occurs. Gallop rhythm, cardiomegaly, and impaired left ventricular function on echocardiography and nonspecific electrocardiographic abnormalities may disclose an earlier stage of the disease. Though the history is usually short (six months to two years) sometimes patients have had cardiomegaly for a number of years, indicating a much longer period of development of the disease.

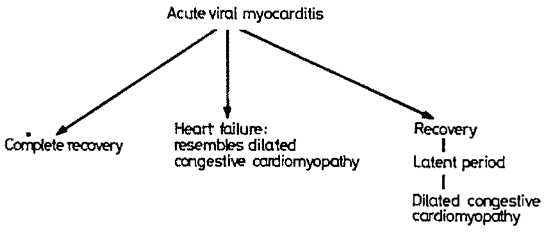
The incidence is largely unknown. Torp[78] reported 94 cases of verified congestive cardiomyopathy in the years 1970–77 in Malmo, Sweden, which has a population of 250 000. This study was part of the research project on congestive cardiomyopathies of the International Society and Federation of Cardiology.[79]

An association between virus disease and dilated congestive cardiomyopathy has been suggested on many occasions.[75 76 80] Recently we investigated the levels of Coxsackie virus titres in the blood of patients with dilated congestive cardiomyopathy compared with controls. There was a highly significant increase and very high levels of antibody titres in the cardiomyopathy patients but not in the controls. This difference, however, was confined to those patients with a short history.[81]

The explanation of these findings is uncertain. It is possible that the association between high Coxsackie titres and cardiomyopathy is a chance one; alternatively, recent infection is a possible, but unlikely, explanation since the endomyocardial biopsy in those patients in whom it is performed did not show any evidence of inflammatory lesion. The most likely explanation in my view is that the infection creates an autoimmune process which leads to progressive myocardial damage. Fowles *et al.*[82] reported a disorder of cellular immunity in patients with dilated congestive cardiomyopathy, but Trueman *et al.*[83] did not find any difference between controls and patients with congestive cardiomyopathy by immunofluorescent techniques, denying the claims of Bolte.[84] An association between myocarditis and cardiomyopathy has been suggested[85] in a description of 10 patients with rapid onset of congestive heart failure of unknown cause apparently resulting from early congestive cardiomyopathy. In all patients, however, endomyocardial biopsy showed evidence of inflammatory myocarditis. Nine were treated with prednisone and azothiaprine, and one with prednisone alone. Five improved, though one died later, and four did not deteriorate. Evidence of improvement was based on non-invasive studies and on invasive investigations and biopsy.

A possible sequence of events is shown in Table 2. Acute virus myocarditis results in complete recovery in the vast majority of patients but in a small percentage heart failure may occur acutely, persist, and be indistinguishable from cardiomyopathy except by endomyocardial biopsy. In other patients there may be a latent period after apparently full recovery during which the autoimmune process develops and results in the established syndrome of cardiomyopathy years

Table 2 *Viral myocarditis and cardiomyopathy*


Acute viral myocarditis
Complete recovery
Heart failure: resembles dilated congestive cardiomyopathy
Recovery
Latent period
Dilated congestive cardiomyopathy

later. Alternatively, some patients may have a genetically determined deficiency in cellular immunity which renders them liable to virus attack on the heart. Further work is needed to confirm or refute these hypotheses[86] which are attractive because they open the mind to the possibilities of treatment.

TREATMENT OF DILATED CONGESTIVE CARDIOMYOPATHY

Treatment is unsatisfactory and will remain so until the causes of the diseases are identified. At the present time general measures such as avoidance of smoking and alcohol and reduction of effort are basic. Experience without proof indicates that the suggestion of Burch *et al.*[87] of prolonged bedrest has some merit.

The usual measures for congestive cardiac failure are required. Digitalis is needed if atrial fibrillation is present and may be prescribed in sinus rhythm, but it is uncertain whether there is any benefit after the first few months of treatment.[88 89] Some improvement may be obtained by the use of vasodilators and inotropic agents. We have found hydralazine to be effective but large doses are needed and side effects are not rare.[90] Isosorbide or prazosin can be used as an alternative to hydralazine. Salbutamol[91] is of value by intravenous infusion in critical severe heart failure, mainly because of peripheral vasodilatation and unloading of the left ventricle but also because of some positive inotropic effects. The tachycardia so produced is a disadvantage, and tachyphylaxis is common. Increase in blood sugar and fall in serum potassium are also disadvantages. Positive inotropic agents such as dobutamine may be used. In extreme situations a combination of nitroprusside with dobutamine may produce improvement, but all too commonly this is only transient. Other vasodilators and new inotropic agents are under investigation.

Anticoagulants are indicated if the patient is confined to bed with oedema or if there is atrial fibrillation.

Beta adrenergic blockade

This controversial treatment has been suggested by workers in Gothenburg in Sweden.[92–94] They claimed clinical and haemodynamic improvement after graded doses of metoprolol. It has been suggested that patients with disproportionate tachycardia who may thus have an excess of catecholamines in the heart may be those most suitable for treatment, but a study from our department[95] did not show any increase in plasma noradrenaline or in sympathetic function before overt heart failure had occurred, though parasympathetic function was impaired. Certainly slowing of the heart and reduction in oxygen demand might be of value. By contrast with the results of the Swedish investigators, Ikram and Fitzpatrick[96] found no benefit from beta adrenergic blockade treatment, but many of their patients (71%) had possible alcoholic cardiomyopathy and were less severe symptomatically than the cases of Swedberg *et al.*[94] In addition, they used a different agent, and the duration of treatment was shorter. The matter is still undecided and further trials are necessary.

The results of the studies by Mason *et al.*[85] suggest that when the duration of heart failure is short (a year or less) and the endomyocardial biopsy shows evidence of inflammatory action, steroids and immunosuppressive drugs may be of benefit. Steroids have not been shown to influence the course of typical congestive cardiomyopathy[97] and when given in acute myocarditis may exacerbate the condition.

Previous work has suggested that patients with appreciable ventricular hypertrophy tend to live longer than those with less; that possibly the agent or agents that affect the myocardium have interfered with contractile function by preventing the binding of calcium by troponin. The result of impairment of contractile function could be ventricular dilatation, increased wall tension, and failure of the DNA/RNA interaction that is needed for hypertrophy.[10 11]

Swedburg *et al.*[93] have suggested that prognosis is improved by beta adrenergic blockade therapy but no definite prognostic improvement has been reported from other methods of treatment though our studies have shown that there was a slight benefit in patients treated in the past two to five years, perhaps as a result of earlier diagnosis and vasodilator treatment (MacArthur *et al.*, to be published).

Restrictive/obliterative cardiomyopathy

Restrictive/obliterative cardiomyopathy is usually caused by endomyocardial fibrosis, either of the tropical variety with little or no eosinophilia or of the temperate zone type with intense eosinophilia, as described by Loeffler in 1936.[15] These two conditions have been regarded as one and the same by Olsen and Spry[98] and have been named Loeffler's endomyocardial disease by the WHO/ISFC task force.[6] Nevertheless, though the pathological features are identical and the clinical and haemodynamic abnormalities closely similar, differences do exist between the two conditions. There is the absence of significant eosinophilia in the tropical type of endomyocardial fibrosis, the climatic differences, and the incidence of tropical endomyocardial fibrosis in the rainy season. There is no climatic incidence or seasonal variation in Loeffler's endomyocardial fibrosis of temperate climate as far as is known.

It has been suggested[86] that the endocardium reacts in the same way to different irritants, producing the exudative reaction leading to fibrosis and thrombosis, with changes in the small intramyocardial vessels that is characteristic of endomyocardial fibrosis. Scarring of the myocardium results and in the late stages fibrous tissue and thrombus progressively obliterate the ventricular cacity and increase the resistance to inflow.

A possible irritant that has been extensively studied is the eosinophil. Clones of circulating eosinophils in Loeffler's endomyocardial disease have structural abnormalities. They are vacuolated and degranulated. The granules are abnormal and may release products which damage the endocardium.[99] There is abnormal binding of IgG coated erythrocytes. A third of the abnormal eosinophils ingest red blood cells that are coated with complement as compared with less than 1% in normal subjects. Also eosinophil kinetics are abnormal and their half life is twice normal. Prolonged retention of eosinophils in the circulation may be an important factor in endomyocardial damage.[98 99]

It may be that the rogue eosinophil is also the cause of tropical endomyocardial fibrosis and studies sponsored by the ISFC are in progress to investigate this.

TREATMENT OF ENDOMYOCARDIAL FIBROSIS

Treatment is unsatisfactory. Attempts to control profuse eosinophilia by means of steroid and immunosuppressive therapy and by antimetabolic drugs have not been strikingly successful,[100] except in acute exacerbations of the disease. Treatment for heart failure is only partly successful because systolic function remains good until a fairly late stage, while severe mitral and tricuspid regurgitation may dominate the picture. Improvement has been achieved by surgical means, consisting of resection of the endomyocardial fibrous tissue and thrombus, and replacement, when needed, of the atrioventricular valves.[101–103] Early results are satisfactory but the long term prognosis is uncertain. Three patients have been treated surgically at the Royal Postgraduate Medical School and have done well initially.[104]

AMYLOID HEART DISEASE

Although rare, amyloid heart disease is an intriguing entity. Because of its distribution around the small blood vessels in the myocardium it produces a stiff unyielding muscle mass; the "stiff heart".[105]

The rigid myocardium causes abnormalities of filling, some of which resemble constrictive pericarditis and restrictive cardiomyopathy. Differences do exist, however, especially in the pattern of ventricular filling. Filling is slow throughout diastole in contrast to endomyocardial fibrosis in which ventricular filling is initially rapid and then becomes slow. This difference explains the absence of a left ventricular third heart sound in amyloid heart disease.[105]

Nevertheless, clinical similarities to constrictive pericarditis or restrictive cardiomyopathy do exist, especially in the pattern of the jugular venous pulse, and amyloid disease should be considered in the differential diagnosis especially if there is cardiac pain.

I have presented some hard data, much personal experience and conviction, and a deal of speculation. I make no apology for the last for it is the business of clinical research workers to ask questions as well as to answer them.

I speculate that hypertrophic cardiomyopathy is an endocrine disorder; that congestive cardiomyopathy is a disease of cellular immunity set up by a previous virus infection; that restrictive/obliterative cardiomyopathy is a disorder of immunity of the eosinophil.

There are many problems to be resolved and the prospects may seem daunting, yet they are, in fact, exciting and challenging and I am sure we will have the answers by the end of the century, though we shall require the collaboration of experts in many fields: immunologists, cell biologists, endocrinologists, biochemists, geneticists, and others.

No longer are the cardiomyopathies the province of the cardiologist alone for their frontiers extend deep into the realms of general internal medicine, pathology, and immunology.

I am grateful to all colleagues who have helped me in this work, in particular Dr W McKenna, Dr R Alvares, Professor R E Steiner, Dr Maurice Raphael, and Dr Derek Gibson.

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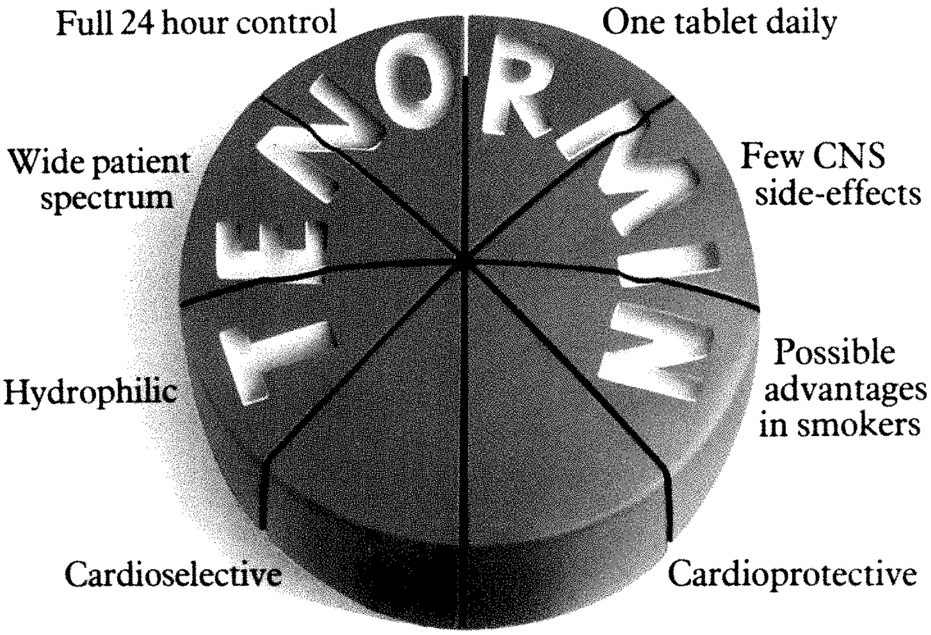

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Haemodynamic effects of nifedipine and propranolol in patients with hypertrophic obstructive cardiomyopathy

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SUMMARY The haemodynamic effects of nifedipine, propranolol, and the combined administration of the two drugs were studied in 12 patients with hypertrophic obstructive cardiomyopathy. The combined administration of nifedipine and propranolol appeared to be superior to that of nifedipine alone. The spontaneous heart rate was reduced in most cases after nifedipine plus propranolol, and at atrial pacing the following results were obtained: left ventricular peak systolic pressure was reduced from 200±39 to 157±30 mmHg; a positive correlation was found between the pre-drug left ventricular end-diastolic pressure and the magnitude of reduction in left ventricular end-diastolic pressure; systolic blood pressure was reduced from 125±31 to 111±27 mmHg, and total peripheral resistance was reduced from 1403±307 to 1160±209 dyne s^{-1} cm^{-5}. The combined administration reduced the resting left ventricular outflow gradient from 76±19 to 45±26 mmHg, while cardiac index was left unchanged. The effects on mean pulmonary arteriolar resistance and mean pulmonary arteriolar and mean pulmonary capillary venous pressure were in most cases slight and insignificant. The results indicate an improved haemodynamic condition in patients with hypertrophic obstructive cardiomyopathy after the combined administration of nifedipine and propranolol: a treatment that might provide a new and useful alternative to already existing medication.

Drugs depresssing myocardial contractility should diminish the degree of left ventricular outflow obstruction in patients with hypertrophic obstructive cardiomyopathy,[1] and medical treatment of this disorder with beta adrenergic receptor blockers has been in use for many years. While propranolol reduces left ventricular outflow (LV-Ao) gradient at rest, on exercise, and during isoprenaline infusion,[2] and improves exercise performance,[3] and relieves the symptoms of angina pectoris,[4-6] the drug neither reduces the incidence of asymptomatic ventricular arrhythmias nor the risk of sudden death.[7-9] Calcium antagonists such as verapamil and nifedipine depress contractile force by inhibiting transmembrane calcium influx during excitation.[10-12] Hereditary hamster cardiomyopathy is thought to be the result of a membrane disease, and abnormal calcium flux probably plays a prominent role in its pathogenesis.[13] The possible relation between this cardiomyopathy and hypertrophic obstructive cardiomyopathy has been discussed.[14] It has been shown that calcium antagonistic drugs, and, to a lesser extent, beta adrenergic receptor blockers are able to prevent the development of heart lesions in hamsters with hereditary cardiomyopathy.[13] Recently, it has been reported that the calcium antagonistic drug verapamil reduces the resting left ventricular outflow gradient, increases the heart rate and cardiac output, and lowers systolic blood pressure in patients with hypertrophic obstructive cardiomyopathy.[15] With long term treatment by this drug exercise tolerance increased, and heart size, QRS complex amplitude, left ventricular outflow gradient, free wall thickness, and left ventricular diameter were reduced.[16 17] The conclusion drawn from one of these studies was that verapamil is superior to beta blockers in hypertrophic obstructive cardiomyopathy.[16]

By reducing the entry of calcium ions into smooth muscle cells, calcium antagonists reduce blood pressure and total peripheral resistance, thereby inducing a reflex sympathetic stimulation of the heart.[18-20] This effect, which is presumed to be present even during chronic administration of nifedipine,[21 22] will probably, to a certain extent, counteract the negative inotropic action of the drugs.[23] A more rational way to treat patients with hypertrophic obstructive car-

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diomyopathy would be to combine a calcium antagonist with a beta adrenergic receptor blocker. Verapamil increases atrioventricular nodal conduction time and refractoriness,[24] and a pronounced and dose related increase in PR interval after this drug has been found in patients with hypertrophic obstructive cardiomyopathy.[15] In addition, sinus arrest and sinus bradycardia associated with oral verapamil treatment have been described in 2% and 11% of these patients, respectively.[25] Because of the tendency to produce atrioventricular block, the combined administration of verapamil and a beta blocker is not recommended.[26 27] On the other hand, nifedipine alone[28 29] or in combination with a beta adrenergic receptor blocker has no detrimental effect on atrioventricular nodal function.[19 30] This paper describes the acute haemodynamic changes in patients with hypertrophic obstructive cardiomyopathy induced by nifedipine, propranolol, and the combination of nifedipine and propranolol.

Patients and haemodynamic measurements

Twelve patients, six men and six women, aged 26 to 67 years (mean 45 years) participated in the study. Before catheterisation a tentative diagnosis of hypertrophic obstructive cardiomyopathy was made on the basis of symptoms, physical examination, and electrocardiographic and echocardiographic abnormalities. The patients were all in normal sinus rhythm. Informed consent was obtained from all. All cardiac medication was discontinued at least three days before catheterisation.

The investigation was carried out with the patients supine and fasted. They were premedicated with 0·1 g aprobarbitone. Right heart catheterisation was performed with a Swan-Ganz thermodilution catheter advanced to the pulmonary artery, and a pacemaker electrode was placed in the right atrium. Cardiac output was measured at least in duplicate by thermodilution. Mean pulmonary arteriolar ($\overline{\mathrm{PA}}$) and mean pulmonary capillary venous pressure ($\overline{\mathrm{PCV}}$) were obtained by electrical integration recorded on a Mingograph 82 (Elema-Schönander, Stockholm, Sweden). Left ventricular peak systolic pressure (LVPSP) and left ventricular end-diastolic pressure (LVEDP) were obtained through an end-hole catheter (multipurpose side-holes, F. 8, Ducor) placed in the apex of the left ventricle by the retrograde femoral technique. The left ventricular-aortic pressure (LV-Ao) gradient was measured by slowly withdrawing the catheter from the apex of the ventricle to the aortic root. Particular care was taken in order to avoid its entrapment. Changes in heart rate induced by exercise, isoprenaline infusion, and atrial pacing may change the left ventricular outflow gradient and left ventricular end-diastolic pressure in patients with hypertrophic obstructive cardiomyopathy[2 31] and, in order to eliminate rate dependent haemodynamic changes, all recordings were performed at an atrial pacing rate about 20 beats above the heart rate in the control period. The patients were then randomised into two groups.

Patients in group 1 were first given nifedipine 20 mg to chew in the mouth and the recordings were repeated 30 minutes later. Propranolol, 5 mg intravenously over five minutes, was then given, and the measurements were repeated 10 minutes after the end of the injection.

Patients in group 2 were given the propranolol first, 5 mg intravenously with measurements 10 minutes later, and then the 20 mg of nifedipine to chew with repeat measurements 30 minutes later.

CALCULATIONS AND STATISTICAL ANALYSIS

Pulmonary arteriolar resistance

$$(\mathrm{PAR}) = \frac{\overline{\mathrm{PA}} - \overline{\mathrm{PCV}}}{\mathrm{CO}} \times 80 \text{ dyne s}^{-1}\text{ cm}^{-5}$$

$$\text{Mean aortic pressure } (\overline{\mathrm{Ao}}) = \frac{\text{systolic BP} + 2 \times \text{diastole BP (mmHg)}}{3}$$

$$\text{Total peripheral resistance (TPR)} = \frac{\mathrm{Ao}}{\mathrm{CO}} \times 80 \text{ dynes}^{-1}\text{ cm}^{-5}$$

$$\text{Cardiac index (CI)} = \frac{\text{CO (l/min)}}{\text{Total body surface (m}^2)}$$

The results are expressed as mean±SD. Student's t test for paired comparison was used when observations before were compared with those after the drugs. Differences were regarded as significant when $p \leqq 0{\cdot}05$.

Results

The spontaneous heart rate for the whole group of patients in the control period was 76±14 beats/minutes (Table 1). Neither nifedipine, propranolol, nor the combined administration of the two drugs significantly changed mean heart rate (Table 1). While nifedipine alone, however, tended to increase heart rate, propranolol and the combined administration tended to decrease it (Table 1).

With atrial pacing, nifedipine and propranolol lowered left ventricular peak systolic pressure in most cases, and the combined administration of the two drugs significantly reduced left ventricular peak systolic pressure for the whole group of patients from 200±39 to 157±30 mmHg ($p<0{\cdot}001$) (Table 1, Fig. 1).

Eight out of 12 patients had a left ventricular end-diastolic pressure in the control period above the normal limit (>12 mmHg). Neither the separate administration of nifedipine, propranolol, nor the

Table 1 *Haemodynamic measurements in control period (C), after nifedipine (N), propranolol (P), and the combined administration of nifedipine and propranolol (N+P, P+N)*

	C_1 (*6 patients*)		*N*		*N+P*	*C_2* (*6 patients*)		*P*		*P+N*	*C_1+C_2* (*12 patients*)		*N+P*
Heart rate (beats/min)	73 (18)	NS	81 (16)	*	66 (6)	79 (9)	NS	70 (13)	NS	70 (10)	76 (14)	NS	68 (8)
LVPSP (mmHg)	197 (55)	**	180 (61)	NS	153 (37)	203 (19)	NS	179 (36)	NS	161 (44)	200 (39)	***	157 (30)
LVEDP (mmHg)	17 (10)	NS	17 (6)	NS	12 (3)	17 (4)	NS	15 (5)	*	17 (2)	17 (7)	NS	15 (4)
SBP (mmHg)	127 (40)	NS	123 (48)	NS	112 (32)	123 (21)	NS	122 (19)	*	108 (23)	125 (31)	*	111 (27)
TPR (dyne s^{-1} cm^{-5})	1413 (310)	**	1050 (217)	**	1138 (252)	1393 (333)	NS	1598 (276)	**	1182 (179)	1403 (307)	**	1160 (209)
LV-Ao gradient (mmHg)	70 (17)	NS	54 (35)	NS	38 (23)	81 (22)	*	57 (30)	NS	52 (30)	76 (19)	***	45 (26)

Asterisks indicate those values that are significantly different (*$p<0{\cdot}05$; **$p<0{\cdot}01$; ***$p<0{\cdot}001$); NS, not significant. SD in parentheses. LVPSP, left ventricular peak systolic pressure; LVEDP, left ventricular end-diastolic pressure; SBP, systolic blood pressure; TPR, total peripheral resistance; LV-Ao, left ventricular outflow.

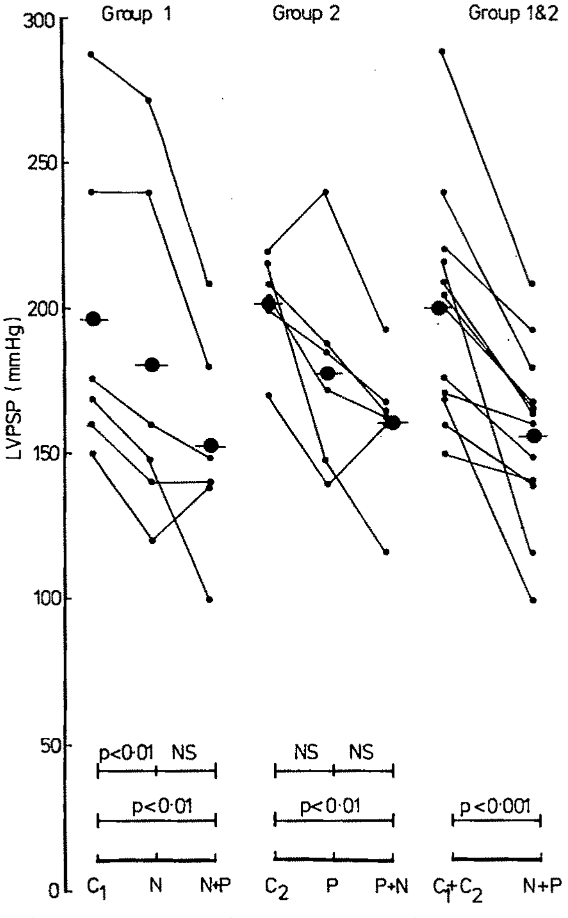

Fig. 1 *Effect of nifedipine (N) and propranolol (P) on left ventricular peak systolic pressure (LVPSP). NS, not significant.*

combined administration of the two drugs significantly changed it (Table 1, Fig. 2); after the combined administration of nifedipine and propranolol, however, the fall in left ventricular end-diastolic pressure (△ LVEDP) was significantly correlated to the pre-drug values (Fig. 3). In the group of six patients initially given nifedipine, the only patient with a very high left ventricular end-diastolic pressure had the filling pressure definitely reduced; in the remaining five patients in whom it was normal or slightly raised, the values were essentially unchanged after the drug was given (Fig. 3).

Systolic blood pressure did not change after the initial administration of nifedipine (Table 1, Fig. 4). Intravenous injection of propranolol to patients not pretreated with nifedipine did not reduce systolic blood pressure (Table 1). The combined administration of the two drugs, however, significantly reduced systolic blood pressure for the whole group ($p<0{\cdot}05$) (Table 1, Fig. 4). Nifedipine reduced total peripheral resistance in all patients, propranolol increased it in most patients; the combined administration, on the other hand, reduced it in all but one, and to a significant degree ($p<0{\cdot}01$) (Table 1, Fig. 5).

The pretreatment resting left ventricular outflow gradient was 76±19 mmHg (range 50 to 114 mmHg) (Table 1). While the separate administration of nifedipine or propranolol reduced the gradient in the majority of patients, the reducing effect of the combined administration was much more significant (Table 1, Fig. 6). In one patient, the gradient increased after the initial administration of nifedipine (from 96 to 120 mmHg), with a simultaneous reduction in systolic blood pressure from 144 to 120 mmHg; after the combined administration, on the other hand, the gradient fell to 80 mmHg (Fig. 6).

Whereas nifedipine significantly increased cardiac index, propranolol reduced it in most cases; the com-

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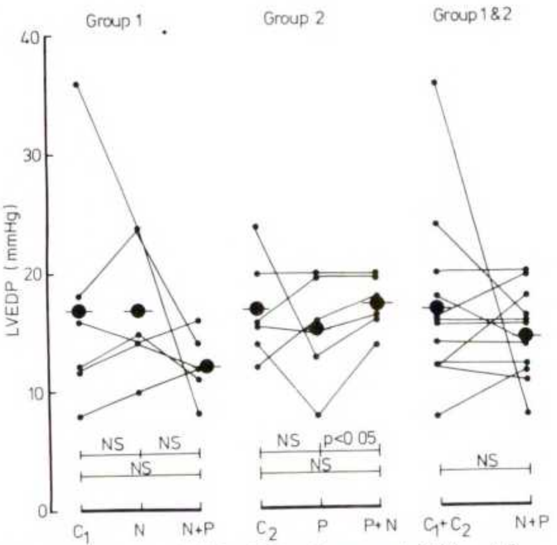

Fig. 2 *Effect of nifedipine (N) and propranolol (P) on left ventricular end-diastolic pressure (LVEDP). NS, not significant.*

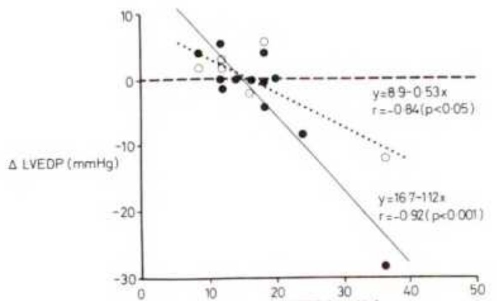

Fig. 3 *Relation between control left ventricular end-diastolic pressure (LVEDP) and change in LVEDP (△ LVEDP) after nifedipine (open circles, interrupted line), and the combined treatment with nifedipine and propranolol (closed circles, solid line).*

bined administration caused a slight and statistically insignificant increase (Table 2, Fig. 7). The individual increases or decreases in cardiac index induced by the separate or combined administration of the drugs were, with few exceptions, associated with a fall or an increase in total peripheral resistance, respectively (Fig. 8).

Mean pulmonary arteriolar pressure was slightly but significantly increased by the combined administration of nifedipine and propranolol (Table 2). Neither nifedipine, propranolol, nor the combined administration of the two drugs significantly changed mean pulmonary arteriolar resistance and mean pulmonary capillary venous pressure (Table 2).

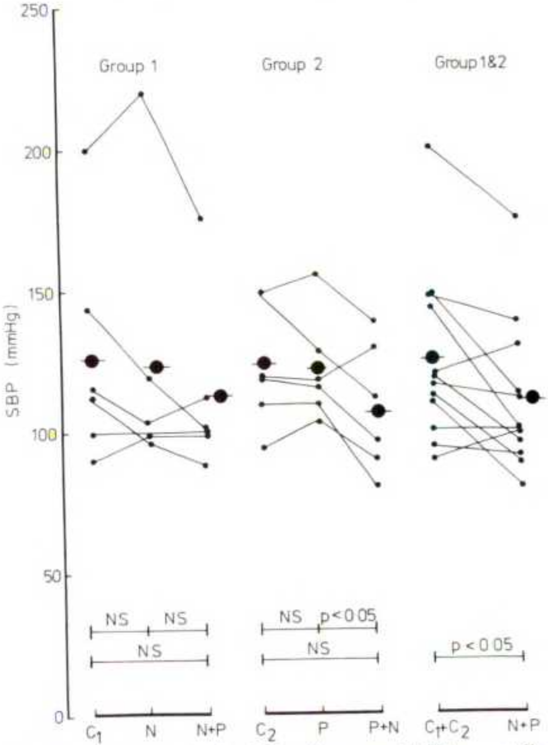

Fig. 4 *Effect of nifedipine (N) and propranolol (P) on systolic blood pressure (SBP). Symbols as in Fig. 2.*

The PR interval on the surface electrocardiogram was neither changed by nifedipine, propranolol, nor by the combined administration of the two drugs.

Discussion

The increase in heart rate induced by nifedipine in most of our patients is caused by a baroreceptor mediated activation of the sympathetic tone,[20 32] an effect that could be completely blocked by intravenous administration of propranolol.

The fall in left ventricular peak systolic pressure after nifedipine is in accordance with previous reports.[23 33 34] This fall was more pronounced when the drug was combined with propranolol. The hypercontractile state in hypertrophic obstructive cardiomyopathy has been related to myocardial calcium overload,[8 15 16] resulting from an abnormality of the cell membrane[8] and/or an increased and abnormal sensitivity to catecholamines,[35] which in that way augments calcium influx.[36-38]

The majority of the patients had raised left ventricular end-diastolic pressures, consistent with earlier reports on patients with hypertrophic obstructive cardiomyopathy.[31] Prolonged left ventricular isovolumic

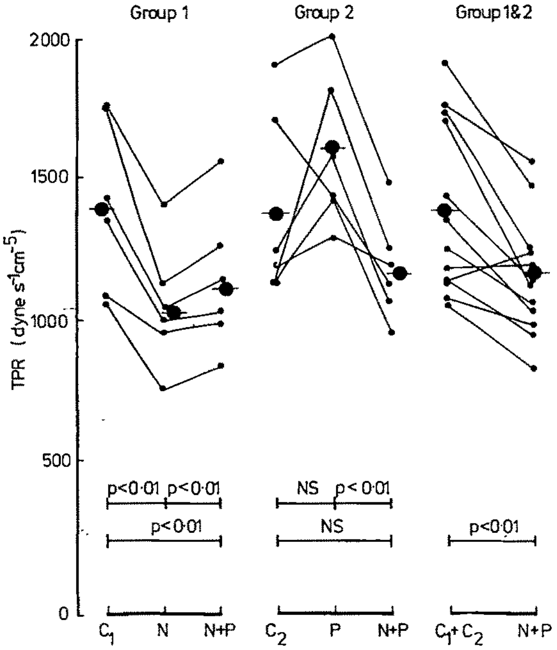

Fig. 5 *Effect of nifedipine (N) and propranolol (P) on total peripheral resistance (TPR). Symbols as in Fig. 1.*

relaxation time, together with an impaired diastolic filling, have also been shown in patients with this malady.[39 40] It has been suggested that the raised left ventricular end-diastolic pressure not only reflects the severity of the disease, but is the main determinant of symptoms and prognosis.[41] While isoprenaline lowers left ventricular end-diastolic pressure in normal individuals as well as in patients with heart disease other than hypertrophic obstructive cardiomyopathy,[42] it has been shown that left ventricular end-diastolic pressure increases after isoprenaline in most patients with that disease.[31] In addition, the administration of isoprenaline to patients with hypertrophic obstructive cardiomyopathy always increases the obstruction to left ventricular outflow and muscular exercise often increases it.[1 2] Our results indicate that nifedipine alone, and in particular the combined administration of nifedipine and propranolol, may improve left ventricular filling and compliance in those patients with increased left ventricular end-diastolic pressure. Recently it has been reported that left ventricular isovolumic relaxation time in hypertrophic obstructive cardiomyopathy was favourably shortened by the administration of nifedipine, 10 to 20 mg sublingually.[43] Though left-sided filling pressure rose after verapamil in a number of patients with hypertrophic obstructive cardiomyopathy, this phenomenon occurred mainly in patients who had normal pressures in the control period.[15]

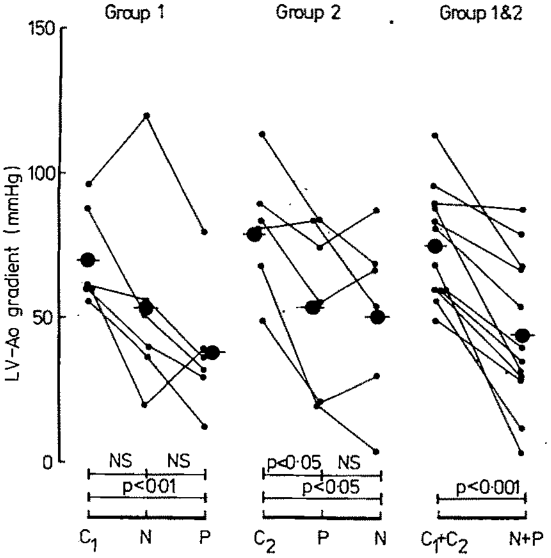

Fig. 6 *Effect of nifedipine (N) and propranolol (P) on resting left ventricular outflow (LV-Ao) gradient. Symbols as in Fig. 1 and 2.*

The effects of nifedipine and the combined administration of nifedipine and propranolol on systolic blood pressure and total peripheral resistance are in accordance with previous observations.[20 32 44]

The effects of nifedipine and propranolol and the combination of the two drugs on mean pulmonary arteriolar resistance and mean pulmonary arteriolar and mean pulmonary capillary venous pressure were in most cases slight and insignificant.

Whereas the separate administration of nifedipine and propranolol reduced left ventricular outflow gradient in most patients, the combined administration of the two drugs caused a more pronounced and general reduction in the gradient in all patients. Any changes in the gradient result from alterations in left ventricular peak systolic pressure and systolic blood pressure. It has been suggested that reduction in systolic blood pressure and total peripheral resistance may increase the left ventricular outflow gradient in patients with hypertrophic obstructive cardiomyopathy,[45] and in one patient this was found after nifedipine. The combined administration, however, reduced the gradient slightly in comparison with the control value.

The nifedipine-induced increase in cardiac index during atrial pacing found in our study is consistent with a previous report.[32] Even in combination with propranolol, which by itself reduces cardiac index,[2] eight out of 12 patients were able to increase their cardiac index in relation to the control values. As heart rate was kept constant by atrial pacing, it is

Table 2 *Haemodynamic measurements in control period (C), after nifedipine (N), propranolol (P), and combined administration of nifedipine and propranolol (N+P, P+N)*

	*C*₁ (*6 patients*)		*N*		*N+P*	*C*₂ (*6 patients*)		*P*		*P+N*	*C*₁+*C*₂ (*12 patients*)		*N+P*
CI (l/min per m²)	3·0 (0·5)	**	3·5 (0·5)	**	3·3 (0·5)	3·1 (0·3)	NS	2·8 (0·7)	**	3·2 (0·5)	3·0 (0·3)	NS	3·2 (0·3)
$\overline{PA}$ (mmHg)	19 (7)	NS	21 (9)	NS	21 (10)	15 (6)	NS	16 (6)	*	19 (6)	17 (7)	*	20 (8)
$\overline{PCV}$ (mmHg)	12 (6)	NS	15 (8)	NS	14 (8)	10 (5)	NS	11 (4)	NS	12 (5)	11 (6)	NS	13 (7)
PAR (dyne s^{-1} cm^{-5})	102 (64)	NS	80 (29)	NS	102 (53)	82 (30)	NS	102 (42)	NS	87 (30)	92 (49)	NS	95 (42)

Asterisks indicate those values that are significantly different (*$p<0·05$; **$p<0·01$); NS, not significant. SD in parentheses. CI, cardiac index; $\overline{PA}$, mean pulmonary arteriolar pressure; $\overline{PCV}$, mean pulmonary capillary venous pressure; $\overline{PAR}$, pulmonary arteriolar resistance.

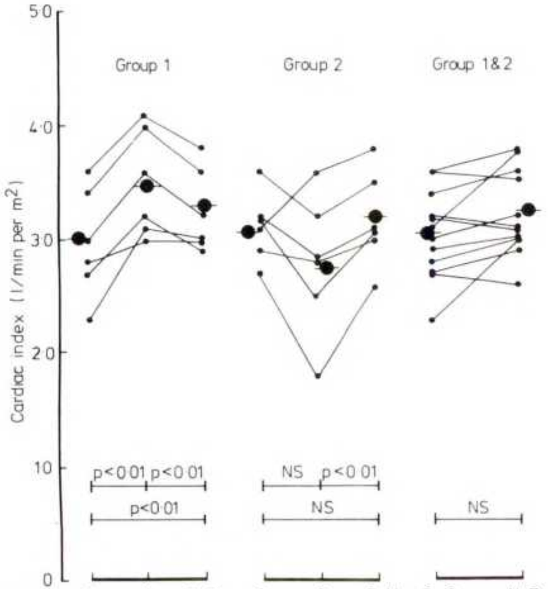

Fig. 7 *Effect of nifedipine (N) and propranolol (P) on cardiac index. Symbols as in Fig. 1.*

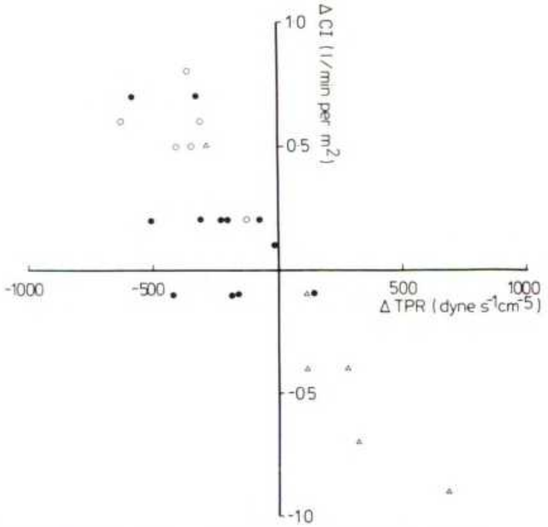

Fig. 8 *Relation between the changes in total peripheral resistance (△ TPR) and cardiac index (△ CI) after nifedipine (open circles), propranolol (open triangles), and the combined administration of nifedipine and propranolol (closed circles).*

probable that the increase in cardiac index observed in all patients after nifedipine and in most patients after the combined administration of both drugs was mainly the result of a reduction in total peripheral resistance (afterload). Even in the patient where the left ventricular outflow gradient increased after nifedipine, a rise of cardiac index from 3·0 to 3·6 l/min per m² was found.

The lowering of left ventricular peak systolic pressure, systolic blood pressure, and left ventricular outflow gradient in the presence of a maintained cardiac index will reduce myocardial oxygen needs and have a favourable effect on the balance between myocardial oxygen supply and demand and also prevent the vicious cycle of obstruction hypertrophy.[2] In this acute haemodynamic study, the combined administration of nifedipine and propranolol appeared to be superior to the separate administration of nifedipine, and the increased sympathetic tone secondary to nifedipine seemed to be well counteracted by beta adrenergic receptor blockade. The combined effects on left ventricular peak systolic pressure, systolic blood pressure, and left ventricular outflow gradients were more pronounced, cardiac index was in most patients maintained at higher levels than in the control period, total peripheral resistance was reduced, and left ventricular end-diastolic pressure was decreased in those patients having high control values. Since an extension of the study would be time consuming and also troublesome to the patients, drug-induced haemodynamic changes were not measured at a spontaneous heart rate. The negative chronotropic action of the combined administration of nifedipine and propranolol will have a favourable effect on myocardial oxygen consumption.[46] No side effects were observed, and no disturbance in atrioventricular nodal function was noted.

Our results indicate that the combined administration of nifedipine and propranolol in hypertrophic obstructive cardiomyopathy provides a new alternative to already existing treatment.

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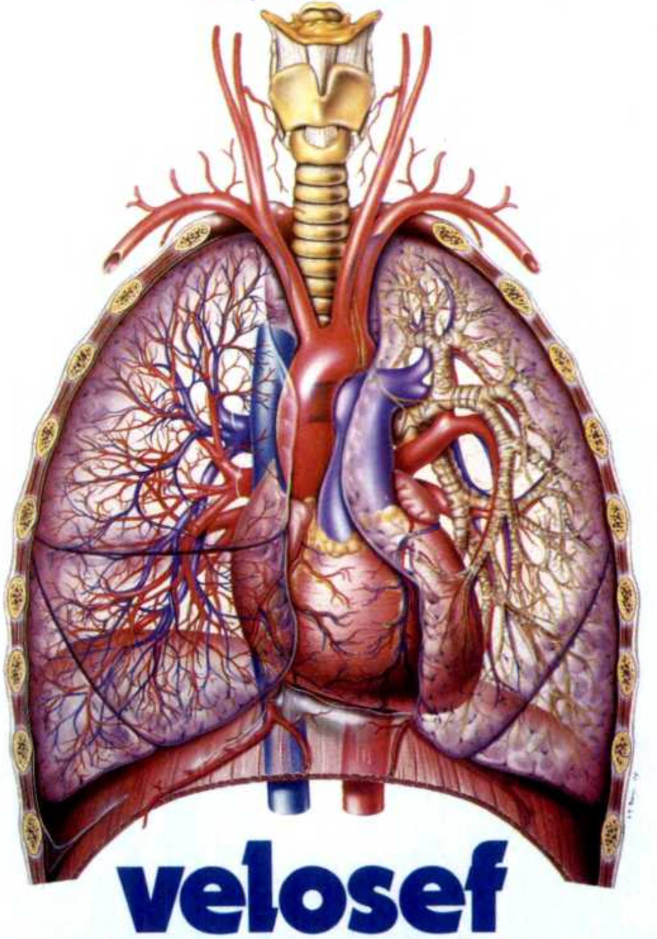

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Br Heart J 1982; **48**: 27–32

Effects of lignocaine on bidirectional tachycardia and on digitalis-induced atrial tachycardia with block

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SUMMARY Most recent studies discussing tachycardias with alternating QRS polarity have referred to those known as *torsade de pointes*. This report, in contrast, deals with bidirectional tachycardia and the effects of lignocaine on 10 patients with this arrhythmia. Three of the patients also had digitalis-induced atrial tachycardia with block. In one patient, a single bolus of lignocaine was followed (five minutes later) by ventricular fibrillation, but the other nine patients received two boluses of 75 mg followed by a drip infusion of 3 mg/min. The drug terminated the episodes of atrial tachycardia with block and bidirectional tachycardia in all patients thus treated. Whereas the abolition of the bidirectional tachycardia was permanent in the seven patients with digitalis intoxication, it recurred after stopping the drip infusion in the two patients without digitalis toxicity. It is concluded that lignocaine can be useful in the treatment of digitalis-induced bidirectional tachycardia and atrial tachycardia with block. From this study no conclusions can be drawn, however, as to whether lignocaine is superior to other class I or class IV agents.

Few papers published during the last 15 years have discussed the treatment of bidirectional tachycardia.[1-7] Since most articles appeared before the use of lignocaine became widespread, it seemed of interest to present our experience with this drug in patients with bidirectional tachycardia, placing additional emphasis on the effects of lignocaine on digitalis-induced atrial tachycardia with block.

Subjects and methods

For the purpose of this paper, bidirectional tachycardia was considered as an electrocardiographic pattern resulting from the existence (or coexistence) of one or more ectopic (atrioventricular junctional or ventricular) rhythms with the following characteristics (Fig. 1)[1-7]: (a) prolonged intraventricular conduction time; (b) QRS morphology different from that (previously or subsequently) produced by supraventricular impulses; (c) standard leads showing alternation in polarity caused by beat-to-beat variations in ÂQRS (from abnormal left axis deviation to right axis deviation); and (d) "incomplete", or "complete", right bundle-branch block pattern in lead V1.

There were 10 patients with bidirectional tachycardia but the effects of properly administered intravenous lignocaine were studied in only nine since in case 1 ventricular fibrillation appeared about five minutes after administration of a single bolus of 75 mg (Fig. 2). In these nine patients an initial 75 mg bolus was followed three minutes later by a second 75 mg bolus, at which time a drip infusion (of 3 mg/min) was started. The infusion was maintained for a seven hour period during which time the patients were continuously monitored in an intensive care unit by trained personnel.

In the Table, however, data from the 10 patients (six men and four women) are presented. The ages of the patients ranged between 43 and 77 years. Four patients with atherosclerotic heart disease and one patient with hypertrophic cardiomyopathy had moderate to severe congestive heart failure. Three patients had chronic lung disease with acute respiratory failure. Two patients had mitral valve prolapse and palpitation caused by documented paroxysmal tachyarrhythmias.

In three patients (Table) His bundle recordings

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Table *Data on patients with bidirectional tachycardia (BT)*

Case No.	*Age (y)*	*Aetiology*	*Clinical digitalis toxicity*	*Serum digoxin (nmol/l)**	*Presumed dosage of digoxin*	*Recurrence of BT 30 min after lignocaine*	*Effects of lignocaine (2 boluses)*	*Effects of lignocaine (drip)*	*Potassium (mmol/l)*
1	69	AHD	?	8·3	?	—	†	—	?
2	77	AHD	Yes	5·8	0·25	No	A of BT	A of PAT	3·9
3	71	AHD	Yes	3·8	0·25 (?)	No	TA of BT	A of BT and PAT	4·2
4	68	AHD	Yes	4·2	0·75	No	TA of BT	A of BT and PAT	4·3
5	63	CLD	No	4·4	0·75	No	None	A of BT	2·9
6	67	CLD	No	2·0	0·75	No	TA of BT	A of BT	2·5
7	61	CLD	No	3·1	1·2	No	None	A of BT	3·1
8	49	C	No	9·0	0·5	No	TA of BT	A of BT	3·9
9	43	MVP	No	NM	?	Yes	None	A of BT	4·2
10	47	MVP	No	NM	?	Yes	None	A of BT	4·4

AHD, atherosclerotic heart disease; CLD, chronic lung disease; C, cardiomyopathy; MVP, mitral valve prolapse; A, abolition; TA, transient abolition; BT, bidirectional tachycardia; PAT, paroxysmal atrial tachycardia with AV block; NM, serum digoxin not measured.

*1 ng digoxin≈1·28 nmol.

†Received only one bolus (see text).

were performed (after explaining the procedure and obtaining informed consent) within the first 60 minutes after the start of the drip infusion. The techniques used in our department to perform these studies have been described previously.[8 9] Plasma concentration of lignocaine was obtained in two patients.

Results

Before lignocaine administration the ventricular rates of bidirectional tachycardia ranged between 140 and 188/min. All 10 patients had alternation between QRS complexes displaying different right bundle-branch block morphologies in lead V1. No patient had a left bundle-branch block morphology in V1. The coexistence of the following independent rhythms could be documented while bidirectional tachycardia was present: sinus rhythm (three patients), paroxysmal atrial tachycardia with block (one patient), and atrial fibrillation (one patient).

Clinical symptoms compatible with digoxin toxicity (nausea and vomiting) were present in three of eight patients without mitral valve prolapse. Plasma digoxin levels were raised 3·8 to 8·9 nmol/l (3 to 7 ng/ml) in six of these eight patients. Digoxin levels were not high in two patients with chronic lung disease (2·0 to 3·1 nmol/l, respectively). The appropriate clinical setting and the low serum potassium levels, however (2·5 and 3·1 mmol/l, respectively), strongly suggested digoxin toxicity.

Plasma lignocaine levels obtained in two patients were as follows: 4 and 4·5 mg/l at the point at which the drip infusions were started; 2·5 and 3 mg/l 30 minutes afterwards; and 2·2 and 2·5 mg/l 90 minutes afterwards.

His bundle recordings performed (in three cases) while the bidirectional tachycardia was occurring intermittently disclosed that in sinus beats there was a properly timed H deflection in front of the corresponding ventricular complexes. The ventricular origin of bidirectional tachycardia was corroborated in two of these patients because the wide QRS complexes were not preceded by H deflections. The remaining patient with *normal* HV intervals in sinus beats (50 ms), however, had *short* HV intervals during bidirectional tachycardia. Fig. 3 (left panel) depicts a short HV interval of 30 ms in the beat having a left posterior hemiblock/"incomplete" right bundle-branch block pattern and an HV interval of 0 ms in the beats with a left anterior hemiblock/"incomplete" right bundle-branch block morphology. This suggested that impulse formation occurred below the His bundle, presumably in two left "fascicular" sites. Conceptually, "fascicular" rhythms (or tachycardias) are "ventricular" since they arise below the bifurcation of the His bundle.[9 10]

EFFECTS OF LIGNOCAINE BOLUSES (Table)

The initial two boluses had the following effects: (a) permanent suppression in one patient; (b) transient abolition with subsequent recurrences in four patients (Fig. 1 and 3); and (c) neither transient nor permanent suppression in four patients (Fig. 4).

EFFECTS OF DRIP INFUSION (Table)

Eight patients still had some episodes of bidirectional tachycardia while the drip infusion of lignocaine was being administered. Whereas in two of these eight patients bidirectional tachycardia was abolished in an "all-or-none" fashion (that is, with both types of complexes disappearing at the same time), in the remaining six patients termination occurred more gradually. The initial disappearance of the alternation in standard leads was replaced by multiform ectopic ventricular beats, some of which had a contour similar

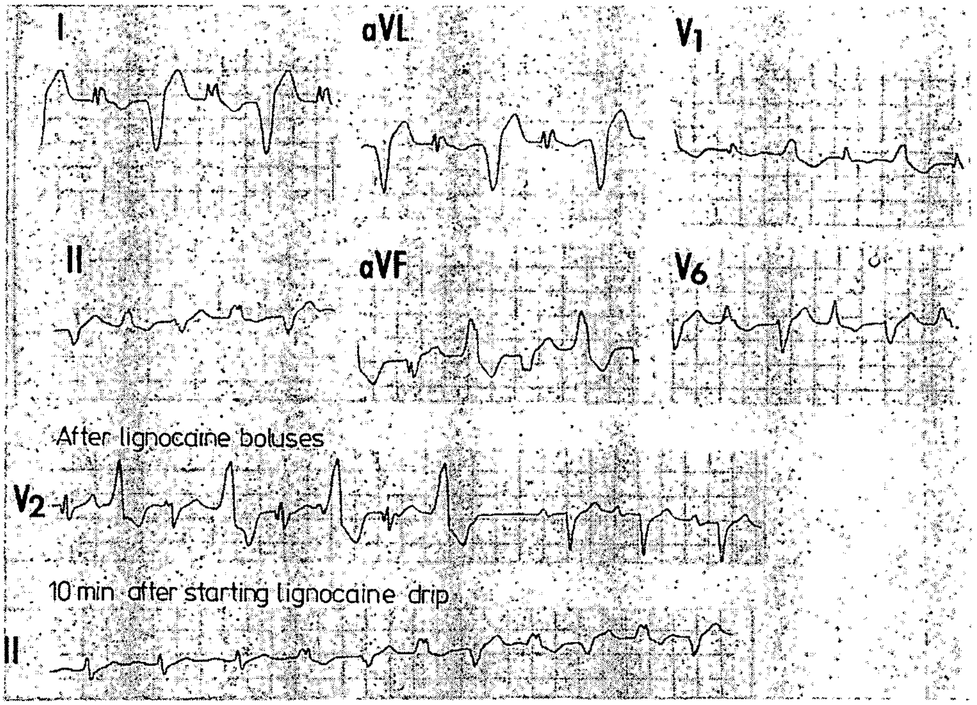

Fig. 1 *The top two rows show the "classic" electrocardiographic pattern of bidirectional tachycardia with alternation in polarity in leads I, II, aVL, aVF, and V6; and alternation in morphology only in lead V1. Bidirectional tachycardia disappeared (temporarily) in the third strip (after the initial two boluses of lignocaine) to reappear 10 minutes after having started the drip infusion.*

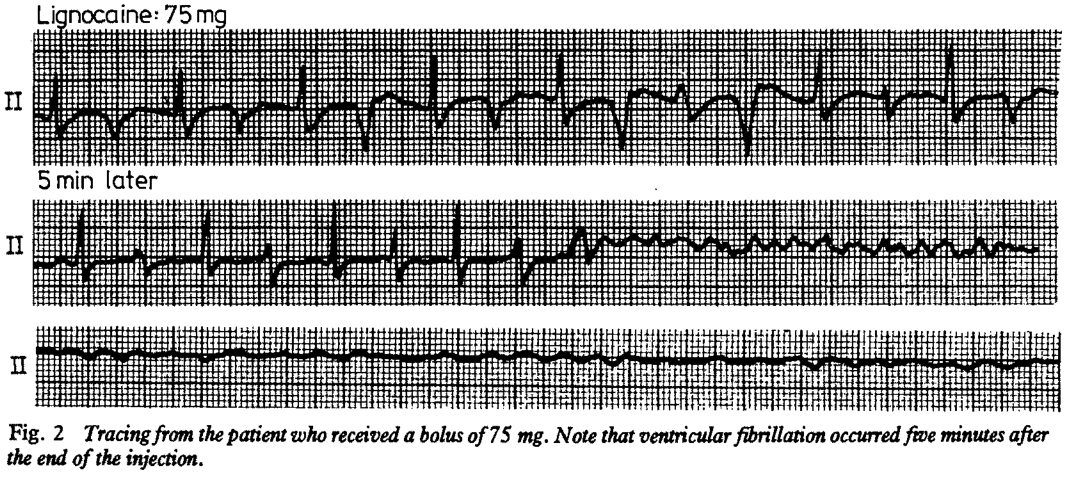

Fig. 2 *Tracing from the patient who received a bolus of 75 mg. Note that ventricular fibrillation occurred five minutes after the end of the injection.*

to that of the ventricular complexes present during bidirectional tachycardia. All episodes of bidirectional tachycardia had gone by between 1·45 and 2·15 hours after the start of the drip infusion. When the bidirectional tachycardia ended five patients had sinus rhythm, one had atrial fibrillation, and three had atrial tachycardia with block. The latter arrhythmia was also suppressed by the drip infusion of lignocaine (Fig. 5). Initially there was a gradual decrease in the ectopic atrial rate which resulted in a change from second degree to 1:1 atrioventricular conduction. Consequently, the ventricular rate increased. As more

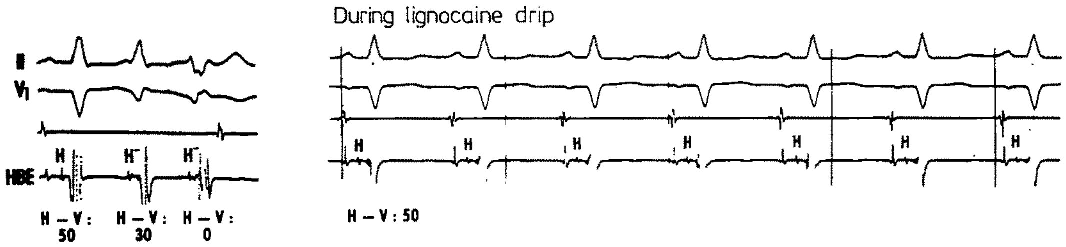

Fig. 3 *His bundle recording obtained 25 minutes (left panel) and one hour (right panel) after having started the drip infusion. The left panel shows a sinus beat followed by the first two beats of the bidirectional tachycardia. Whereas the first (apparently normal for this patient) HV interval is 50 ms, the HV intervals of the second and third (ectopic) beats are shorter than normal (30 and 0 ms, respectively). The latter, when associated with an "incomplete" right bundle-branch block "pattern" in lead V1, suggests a "fascicular" (ventricular) origin.*

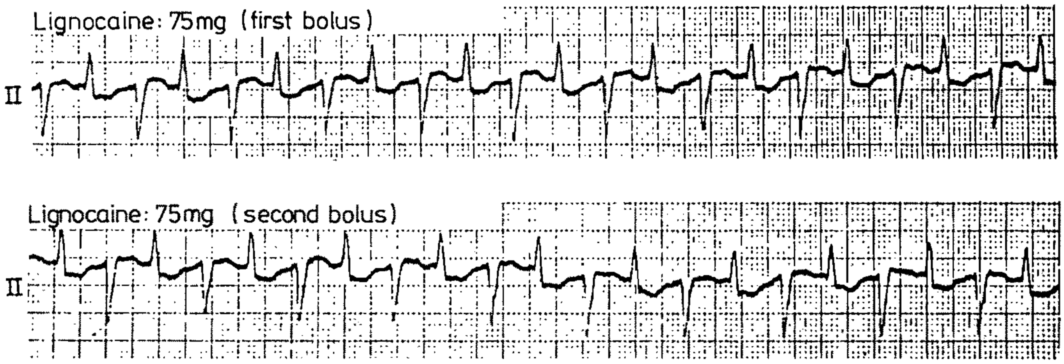
Lignocaine: 75mg (first bolus)
II
Lignocaine: 75mg (second bolus)
II

Fig. 4 *Bidirectional tachycardia not abolished by the initial two boluses of lignocaine.*

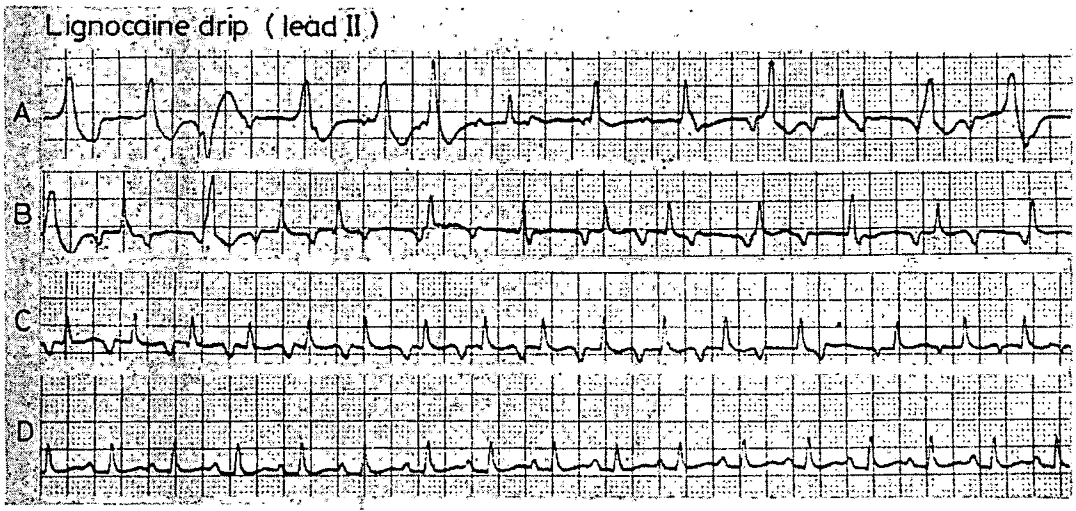

Fig. 5 (same patients as in Fig. 4) *Effects of the drip infusion of lignocaine on the atrial tachycardia with block (caused by digoxin toxicity) which became manifest after bidirectional tachycardia was abolished. These effects were similar to those which had been previously reported with the use of intravenous potassium and procainamide.*[18]

lignocaine was infused, the atrial (and ventricular) rates became progressively slower until the sinus node was able to take over.

After stopping the lignocaine drip (at the end of six hours) six patients had a 60 minute period of sinus rhythm without ventricular ectopic activity. Unifocal ventricular extrasystoles still occurred, however, in the two patients with mitral valve prolapse. Paroxysms of bidirectional tachycardia recurred 30 to 40 minutes later in these two patients. In the remaining patient (with chronic atrial fibrillation) it could not be determined if the wide QRS complexes that were present resulted from aberration of supraventricular impulses or from ectopic ventricular activity. These wide ventricular complexes did not resemble the QRS complexes which had constituted the bidirectional tachycardia.

Discussion

SITE OF ORIGIN OF BIDIRECTIONAL TACHYCARDIA

All published reports dealing with intracardiac studies in patients with *ectopic* bidirectional tachycardia have shown its infra-atrioventricular junctional (ventricular) origin.[1–7 9 10] This finding was corroborated by His bundle recordings in three of our patients.

EFFECTS OF LIGNOCAINE

Lignocaine (a class I agent) was used because in our hospital this is the drug first administered to treat those arrhythmias initially diagnosed as "ventricular". Thus, no conclusions can be drawn as to whether lignocaine is superior to potassium salts, drugs that cause depression of slow inward calcium current, or other class I agents such as diphenylhydantoin, procainamide, and quinidine.[11]

Class I agents act essentially by depressing the fast inward sodium current (fast response).[11] They decrease action potential amplitude, prolong the effective refractory period, and depress phase 4 depolarisation. Lignocaine and diphenylhydantoin, however, shorten action potential duration while procainamide and quinidine lengthen it.[11]

According to Vaughan-Williams, lignocaine shortens action potential duration in those fibres where it was previously longest. Hence, action potential duration becomes more uniform.[11] This effect, combined with the depression of phase 4 depolarisation, may have been responsible for the suppression of the arrhythmias occurring in our patients (which could have resulted from the association of automaticity and conduction disturbances).

In all cases, lignocaine proved to be effective when it could be administered adequately according to its well known pharmacological properties.[12–15] The clinical course, and the plasma concentrations of lignocaine that were observed in two patients, suggested that the effectiveness of this drug was indeed related to its pharmacokinetics.[13 15] For example, it is known that after a single intravenous injection, lignocaine follows a two-compartment exponential disappearance curve.[14] Diffusion through the body from the central compartment is first order, with a distribution half time of five to 10 minutes, equilibration through the body thereby requiring 20 to 40 minutes. The elimination of half time is around two hours.[15]

Case 1 developed ventricular fibrillation five minutes after a single dose of lignocaine. It is possible that ventricular fibrillation occurred at a time when "subtherapeutic" plasma lignocaine levels were present.

The two patients with drug-unrelated bidirectional tachycardia had milder symptoms than those with digitalis-induced arrhythmias. Furthermore, bidirectional tachycardia recurred after stopping lignocaine. Thus, more studies of these types of bidirectional tachycardia appear warranted.

Lignocaine is generally not considered to be a useful drug in the treatment of supraventricular arrhythmias.[16 17] This study showed, however, that it was capable of abolishing atrial tachycardia with block caused by digitalis toxicity. Moreover, the electrocardiographic effects were similar to those produced by intravenous potassium and procainamide, as previously reported by Lown *et al.*[18] The initial effect of lignocaine, potassium, and procainamide is a decrease in the atrial rate which, when of sufficient magnitude, converts the second degree atrioventricular block into 1:1 atrioventricular conduction, thereby increasing the ventricular rate. This gradual decrease in the atrial rate (and therefore of the ventricular rate) continues until the sinus node takes over.

As stated by Lown *et al.*,[18] the infusion should not be stopped when the ventricular rate increases. On the contrary, it has to be continued since this is the response expected before conversion to sinus rhythm.

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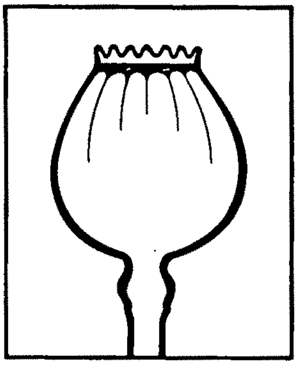

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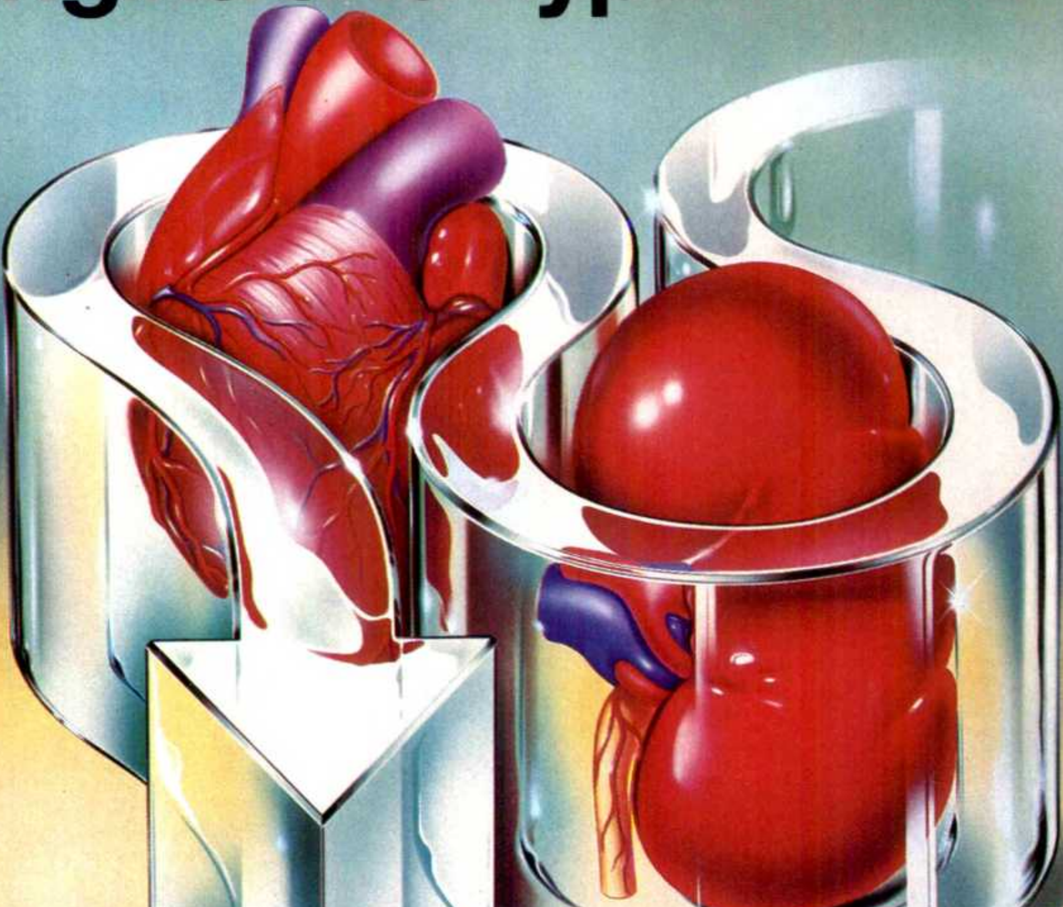

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Br Heart J 1982; **48**: 33–8

Influence of beta adrenergic blockade on effects of physical training in patients with ischaemic heart disease

L VANHEES, R FAGARD, A AMERY

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SUMMARY Reduction in heart rate during submaximal exercise is often used to judge the progress of patients with ischaemic heart disease in the course of a physical training programme. Some patients, however, are treated with beta adrenergic blocking drugs and it remains controversial if chronic beta blockade influences the effects of training and if heart rate remains a useful guide in the evaluation of the state of training of these patients.

Male postinfarction patients, 15 treated with and 15 without beta blockers, were trained for three months, three times a week. Cardiorespiratory results from uninterrupted incremental exercise tests before and after training were compared. In each subgroup, the heart rate and systolic blood pressure were significantly reduced. For heart rate the decrease after training became more pronounced with increasing work load and the overall reduction was significantly less in the beta blocker group compared with the patients not treated with beta blockers. For systolic blood pressure the training-induced reductions were more pronounced in the patients on beta blockers.

The increase of peak oxygen uptake was similar in the patients with and without beta blockers, namely 36% and 34·5%. At submaximal exercise carbon dioxide output, pulmonary minute ventilation, and the respiratory exchange ratio were lower after training, and these effects of training were similar whether or not the patients were on beta blockers.

The study shows that the usual effects of training are observed in patients on beta blockers, and that heart rate remains a useful guide to their evaluation throughout a physical training programme.

The cardiorespiratory effects of physical training have been intensively studied in normal subjects and include increases in both maximal oxygen uptake and maximal pulmonary ventilation, an increase in the anaerobic threshold, and reductions in heart rate and possibly blood pressure at rest and at submaximal work.[1]

Physical training has been used in the rehabilitation of patients with ischaemic heart disease, with roughly similar cardiorespiratory effects.[2 3] The reduction in heart rate during submaximal work is often used to judge the progress of the patient during the programme. Some of these patients, however, are taking beta adrenergic blocking drugs for hypertension, angina, or other disorders. It remains controversial if chronic beta blockade influences the effects of training and if heart rate remains a useful guide in the evaluation of the state of training of these patients.[4 5]

Therefore, in the present study, we compare the cardiorespiratory effects of training in two groups of patients with ischaemic heart disease: one group treated with beta blockers and the other without.

Subjects and methods

(1) SUBJECTS

The study was performed on male patients who were referred to the cardiac rehabilitation unit eight or more weeks after they had suffered from a myocardial infarction. Thirty patients were studied and they all fulfilled the following criteria: no alteration of medication during the training programme, nor for at least six weeks before the pretraining test; no limitation by angina pectoris during pre- and post-training evalua-

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tion and attainment of a work level of at least 110 Watts at the pre-training test. Their characteristics are given in Table 1. Fifteen patients were on beta blockers, and their characteristics were similar to those of the patients without these drugs. The doses of beta blocking drugs are given in Table 2.

(2) TRAINING PROGRAMME

The physical training programme was designed so that the patients would exercise indoors for three months, three days a week for a total duration of 75 minutes, rest included, for each exercise session. Each session consisted of: cycling for 10 minutes, rowing twice for two and a half minutes, running twice for four minutes, and callisthenics twice for 15 minutes. The intensity of the exercise was adapted to 60 to 80% of the measured maximal capacity for each patient. An exercise leader and a physician supervised all exercise sessions.

(3) TESTING PROCEDURES

(a) *General outline*

Testing before and after training was performed using uninterrupted graded exercise on an electromagnetically braked cycle ergometer (Elema Schönander EMT 369), in an air-conditioned laboratory (temperature 18 to 22°C, humidity 40 to 60%), according to an identical procedure. Each subject was tested at approximately the same time of the day before and after training, mostly in the afternoon. Observations were made after 10 minutes sitting on the bicycle (RS) and at several work levels: the patients first exercised at 20 Watts for four minutes and then the exercise rate was increased by 30 Watts every four minutes. All the patients were allowed to perform a symptom limited graded exercise test, that is they determined the point of interruption themselves from their subjective feelings (exhaustion, dyspnoea, pain, or tiredness in the legs). It was not felt acceptable to encourage them any further in view of their ischaemic heart disease. Their final values are indicated as "peak" values.

(b) *Cardiorespiratory variables*

The patient's electrocardiogram was monitored via a high persistence oscilloscope, and heart rate was calculated continuously. Systolic blood pressure was measured with a standard mercury sphygmomanometer. The product of heart rate and systolic blood pressure (rate pressure product) was calculated.

(c) *Respiratory variables*

Pulmonary minute ventilation (V_E) was measured with a pneumotachograph and expressed in l/min, BTPS conditions (body temperature, barometric pressure, saturated with water vapour), oxygen concentration by a paramagnetic oxygen analyser, and carbon dioxide concentration by an infrared carbon dioxide analyser (Siregnost FD 80, Siemens). Oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$), expressed in l/min, were continuously calculated and reduced to STPD conditions (standard temperature and pressure, dry). The respiratory exchange ratio ($R=\dot{V}CO_2/\dot{V}O_2$) and the respiratory equivalent for oxygen ($RE=V_E/\dot{V}O_2$) were calculated. A definition of these variables is given in the "glossary on respiration and gas exchange".[6]

Table 1 *Characteristics of patients*

	Patients treated with beta blockers	*Patients without beta blockers*
No.	15	15
Age (y)*	49·00±2·2	50·50±1·4
Weight (kg)*	73·00±1·5	70·10±2·1
Height (m)*	1·74±0·01	1·72±0·02
Body surface area (m^2)*	1·87±0·03	1·83±0·03
Time between infarction and onset of training (wk)*	27·60±6·3	15·20±3·5
Duration of training (wk)*	13·90±0·5	13·60±0·4
Frequency of training per week*	2·51±0·1	2·41±0·1

*The data are means±SE.
There are no significant differences between the groups for any of the variables.

(4) ANALYSIS OF DATA

The data were analysed separately for the patients treated with and those without beta blockers, at rest in the sitting position, at the work rates of 20, 50, 80, and 110 Watts which were performed by all, and at the final work rate.

For statistical analysis, observations during the last five minutes in the sitting position were used, and during exercise the data of the last minute at each

Table 2 *Details of treatment in patients*

	Patients treated with beta blockers	*Daily dose*	*Patients without beta blockers*
Alprenolol hydrochloride	1	200 mg	0
Atenolol	2	100 mg in 1 200 mg in 1	0
Metoprolol	7	75 mg in 1 100 mg in 4 200 mg in 2	0
Propranolol	5	30 mg in 1 60 mg in 3 120 mg in 1	0
Anticoagulants	3		4
Antihypertensives	2		2
Aprindine	0		3
Digitalis	4		5
Diuretics	2		0
Kinidine	0		1
Nifedipine	0		1
Glyceryl trinitrate	6		3
Sedatives	6		4

exercise level. Unpaired t tests were used to evaluate possible differences between both groups of patients, paired t tests, and analysis of variance to compare pre- and post-training observations.[7] The dispersion of the data is given by standard error of mean.

Results

(1) OBSERVATIONS AT REST AND SUBMAXIMAL EXERCISE

(a) *Cardiovascular variables*

Pre-training heart rate was lower in the patients on beta blockers when compared with those without such treatment as indicated by the lower heart rates at RS-11 beats/min ($p<0.05$), at 20 W-10 beats/min ($p<0.05$), at 50 W-10 beats/min ($p<0.05$), at 80 W-12 beats/min ($p<0.01$), and at 110 W-16 beats/min ($p<0.001$) (Fig. 1). Pre-training systolic blood pressure was not significantly different in the treatment groups.

Training reduced both heart rate and blood pressure. Fig. 1 summarises the absolute levels of heart rate. In Fig. 2 the changes from the pre-training test

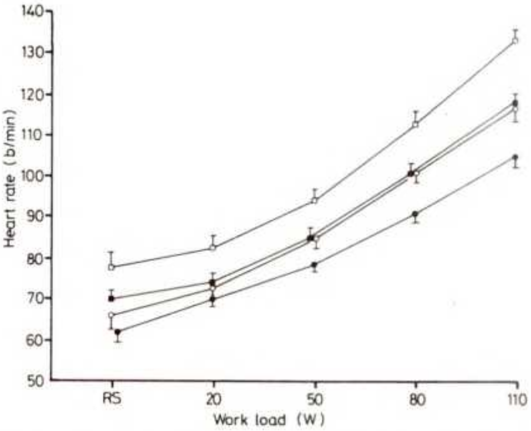

Fig. 1 *Heart rate before (open signs) and after training (closed signs) in patients treated with beta blockers (circles) and in those without beta blockers (squares) at rest in the sitting position (RS) and at 20 W, 50 W, 80 W, and 110 W. Values are means ±SE.*

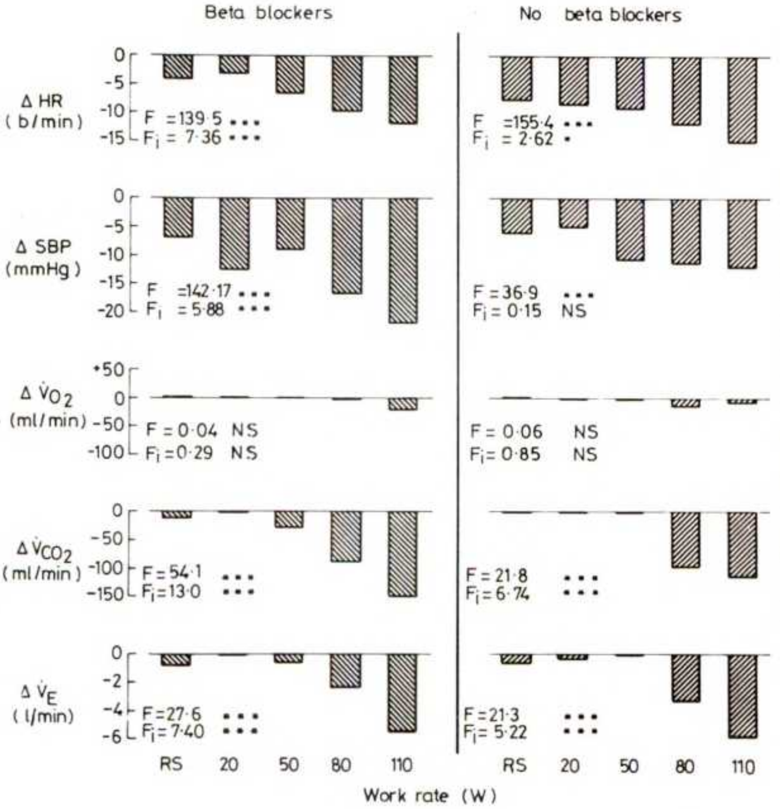

Fig. 2 *Data are analysed by three way analysis of variance, that is for all work loads combined. Training-induced changes of the heart rate (HR), systolic blood pressure (SBP), oxygen uptake (VO_2), carbon dioxide output (VCO_2), and pulmonary ventilation (V_E) at rest in the sitting position (RS) and at 20 W, 50 W, 80 W, and 110 W for both treatment groups. Values are means. F represents the F value for the effect of training on the studied variable (analysis of variance), F_i (F interactions) the F value indicates if there is a significant effect of the level of physical activity on the effect of training. The p values indicate the significance of the F and F_i values. *$p<0.05$; **$p<0.01$; ***$p<0.001$.*

Table 3 *Comparison of peak data of cardiorespiratory variables at symptom limited maximal exercise before and after training for patients treated with and without beta blockers (values are means ±SE)*

	Patients treated with beta blockers (n=15)		*Patients treated without beta blockers (n=15)*	
	Before training	*After training*	*Before training*	*After training*
HR (beats/min)	124±3·6	135±3·5**	137±4·3	148±4·3*
SBP (mmHg)	186±6·3	190±6·8	175±9·2	189±6·8*
RPP (beats/min×mmHg)	23106±1260	25530±1179*	23595±1513	27508±1375*
VO_2 (ml/min)	1627±59	2213±89***	1521±57	2044±60***
VCO_2 (ml/min)	1721±78	2403±131***	1637±61	2232±83***
V_E (l/min)	50·4±2·1	70·4±3·4***	50·5±1·9	70·9±3·6***
R	1·04±0·03	1·08±0·02	1·08±0·01	1·11±0·02
RE	29·6±1·5	31·9±1·0	33·8±1·6	35·2±1·4

P values are given for the comparison of pre- and post-training values within each group: *p<0·05; **p<0·01; ***p<0·001.
Abbreviations: HR, heart rate; SBP, systolic blood pressure; RPP, rate pressure product; VO_2, oxygen uptake; VCO_2, carbon dioxide output; V_E ventilation; R, respiratory exchange ratio; RE, respiratory equivalent for oxygen.

to the post-training evaluation for heart rate and systolic blood pressure, at rest in the sitting position and at 20, 50, 80, and 110 W are illustrated for both subgroups. For resting and exercise data (20 W to 110 W) combined, the 95% confidence limits of the training-induced reductions in heart rate and in systolic blood pressure were, respectively, 6·2 to 8·6 beats/min and 11·4 to 15·8 mmHg for the patients on beta blockers and 8·8 to 12·1 beats/min and 6 to 11·5 mmHg for those without such treatment. These changes were significant (p<0·001 for all) in each subgroup, when three-way analysis of variance was applied, taking (1) resting and exercise conditions (levels of physical activity), (2) subjects, and (3) training into consideration. In general the effects of training appear to be more pronounced with increasing levels of physical activity. When the two subgroups were compared it was found that the training-induced changes of heart rate in the beta blocked group were significantly (p<0·01) less than in the group without beta blockers. The changes of systolic blood pressure, however, were more pronounced (p<0·05) in the beta blocked group.

(b) *Respiratory variables*

Fig. 2 also illustrates the differences for oxygen uptake, carbon dioxide output, and pulmonary ventilation from pre- to post-training for the two subgroups. The observations were similar and statistically not different in patients with and patients without beta blockers. Whereas the oxygen uptake was not affected by training, carbon dioxide output and pulmonary ventilation remained unchanged at 20 and 50 W, but decreased at 80 and 110 W, reflected by the significant interactions between the levels of physical activity and the training effect (all significant at p<0·001). The respiratory exchange ratio was significantly reduced by 7·5% at 80 W and by 8·8% at 110 W for the group receiving beta blockers and by 6·2% at 80 W and 7·7% at 110 W in the group not on beta blockers; no significant differences were observed at the other work rates.

(2) OBSERVATIONS AT SYMPTOM LIMITED MAXIMAL EXERCISE

Table 3 summarises the peak data for the two treatment groups. Heart rate, rate pressure product, oxygen uptake, carbon dioxide output, and pulmonary ventilation were significantly increased in both subgroups after training. The increase of systolic blood pressure was only significant in patients without beta blockers. The respiratory exchange ratio and the respiratory equivalent for oxygen were not different before and after training. Overall the results were similar and not significantly different for the patients with and those without beta blockers.

Discussion

(1) EFFECTS OF TRAINING

The data demonstrate the effectiveness of the training programme and are in agreement with previous reports on physical training in normal subjects and in cardiac patients.

At rest and at submaximal levels of exercise, heart rate, systolic blood pressure, and the rate pressure product were reduced, which is in agreement with previous reports,[8-13] except for systolic blood pressure in some studies.[14 15] In both groups the patients were able to support a higher level of cardiac work since the peak values of these variables were higher after training compared with before training, whereas the respiratory exchange ratio and the respiratory equivalent for oxygen were not statistically different. After training the pre-training peak values of the rate pressure product were reached at a 21% higher oxygen uptake. This suggests that after training, a higher work rate can be attained with a similar myocardial oxygen consumption, since the product of heart rate and systolic blood pressure is well correlated with the oxygen uptake of the heart.[16]

Total body oxygen uptake at submaximal work is not affected by training, in agreement with an unchanged mechanical efficiency.[2 3 17] From 80 W on, however, carbon dioxide output, pulmonary ventilation, and the respiratory exchange ratio were lower after training, suggesting a reduced contribution of anaerobic metabolism to the energy production.[18] Peak oxygen uptake increased significantly after training by, on average, 35% in both groups. Since the subjects could attain a similar respiratory exchange ratio, carbon dioxide output and consequently pulmonary ventilation attained higher values, a well recognised effect of training.[15]

(2) EFFECTS OF BETA ADRENERGIC BLOCKADE

Fifteen patients were on treatment with beta adrenergic blocking agents for at least six weeks before the study. Since heart rate was not measured during a similar exercise test before the drug was started, the degree of beta blockade cannot be ascertained; however, the pretraining heart rate of these patients in the sitting position at rest, which averaged 66 beats/min, is 15% lower than the heart rate of the patients who did not receive beta blockers. Overall these data show that training effects can be achieved in patients on beta blockers. This indicates that the intensity of exercise during the training sessions is adequate. It has been suggested that beta blockers limit exercise capacity.[19] Our data cannot answer this problem but at least a sufficient degree of exercise intensity can be achieved to obtain training effects.

(a) *Respiratory variables*

Beta adrenoceptor blockade did not influence the effects of training on the respiratory variables which is in accordance with Obma *et al.*[5] but not with Malmborg *et al.*[4] The number of patients in the latter study was small, however, and the training intensity low. In the present study the effects of training on aerobic and anaerobic metabolism were similar whether or not the patients were treated with beta blockers. This is in accord with studies of Wasserman *et al.*[20] who showed that neurogenic factors did not play an important role in the ventilatory control during exercise.

(b) *Cardiovascular variables*

Endurance training reduced heart rate, which is considered the result of altered sympathetic-parasympathetic tone. Parasympathetic blocking agents such as atropine have been shown to increase the pre- and post-training heart rates to a similar extent at rest,[21] but the increase at submaximal exercise was greater after training; these findings suggest an increased parasympathetic tone in response to training, at least during exercise. An augmented vagal tone was also shown in trained rats.[22 23] On the other hand, the reduction of heart rate by the beta adrenoceptor blocker propranolol was less pronounced after than before training, suggesting reduced sympathetic tone after training,[21] which is in accordance with the observed decrease of plasma noradrenaline levels.[24 25]

In the present study heart rate decreased significantly after training in patients on chronic treatment with beta adrenoceptor blockers, and the decreases of heart rate were close to, though significantly smaller than those of patients without such treatment. Since beta adrenoceptors were blocked throughout the study, though probably incompletely in a clinical setting, an increase of the parasympathetic tone is a more likely explanation for the observed exercise-induced bradycardia. The many other mechanisms which have been postulated such as ventricular hypertrophy, decreased sensitivity of cardiac adrenergic receptors, and intrinsic changes of the sinus node, can, of course, not be excluded.

The study thus shows that beta blockade does not influence the effects of physical training on various respiratory variables and that heart rate remains a useful guide for the evaluation of patients with ischaemic heart disease on treatment with beta adrenoceptor blockers throughout a physical training programme, provided that the degree of beta blockade remains unchanged.

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Scintigraphic study of relation between left ventricular peak systolic pressure and end-systolic volume in patients with coronary artery disease and normal subjects

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SUMMARY We have studied the relation between left ventricular peak systolic pressure and end-systolic volume in 12 normal subjects and 12 patients with coronary artery disease. Peak systolic pressure was measured with a cuff sphygmomanometer and left ventricular volumes were determined by radionuclide ventriculography.

Observations were made at rest, after 1 mg atropine, and during at least three increments of an infusion of phenylephrine which raised systolic blood pressure by 45 mmHg while heart rate was held constant.

The relation between peak systolic pressure and end-systolic volume at a constant heart rate was found to be linear in all subjects. The slope of this line was steeper in normal subjects than in patients with coronary artery disease and correlated exponentially with the ejection fraction determined simultaneously. The end-systolic volume extrapolated to zero pressure (V_0) was not significantly different between the two groups and correlated poorly with the ejection fraction.

The simple ratio of peak systolic pressure to end-systolic volume, at rest and after drug interventions, was of similar sensitivity to the ejection fraction in the detection of patients with left ventricular dysfunction caused by coronary artery disease. In normal subjects, however, this ratio rose after atropine whereas the ejection fraction was unchanged.

The apparent superiority of the ratio of peak systolic pressure to end-systolic volume over the ejection fraction in the detection of the positive inotropic response to increasing heart rate, coupled with the linearity of this relation over a wide range of systolic blood pressure, suggests that the systolic pressure–volume relation will prove useful in the evaluation of cardiac drug effects in man.

None of the indices derived from the systolic pressure volume relation, however, was more sensitive than the ejection fraction derived simultaneously, in the detection of patients with left ventricular dysfunction resulting from coronary artery disease.

The relation between left ventricular pressure and volume at end-systole in experimental models has been shown to be a sensitive and relatively preload-independent index of the prevailing inotropic state.[1-3]

The utility of this relation as a putative index of inotropic state in man has been enhanced by the finding that peak systolic pressure can be substituted for end-systolic pressure without significantly altering these properties.[4-6]

Considerable interest has thus been shown in this relation, both as a method of studying cardiac drug effects and also as a means of detecting myocardial dysfunction caused by coronary artery disease.[4-10]

The simple ratio of peak systolic pressure to end-systolic volume (P/V ratio), the slope of this relation over a physiological range of blood pressure (P/V slope), and the theoretical value of end-systolic volume extrapolated to zero systolic pressure (V_0) have

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all been used to represent the end-systolic pressure-volume relation, but none has been widely evaluated in man.

We have therefore undertaken a scintigraphic study in normal subjects and patients with coronary artery disease: (i) to confirm the linearity of the peak systolic pressure—end-systolic volume relation in man by a method that does depend on geometric assumptions about ventricular morphology at end-systole; (ii) to compare the P/V ratio, the P/V slope, and V_0—all derived at a constant inotropic state—with the ejection fraction obtained simultaneously; (iii) to compare the sensitivity of these indices in the detection of impaired myocardial function resulting from coronary artery disease.

Subjects and methods

The study was undertaken in 24 normotensive male volunteers. Twelve subjects (mean age 51, range 41 to 69 years) had sustained a myocardial infarction at least six months previously, as evidenced by a typical history of chest pain, raised serum creatine kinase levels, and characteristic electrocardiographic changes (for complete clinical details, see Table 1). No patient had clinical evidence of valvular heart disease or peripheral vascular disease and none had taken any drugs except diuretics within 48 hours of the study.

The other 12 subjects were normal (mean age 34, range 19 to 58 years) with no clinical evidence of cardiovascular disease. They were taking no drugs and had no abnormalities on resting or exercise electrocardiograms. Written informed consent was obtained from all subjects and the procedure was approved by the Human Subjects Committee of the University of California, San Diego. Neither smoking nor the consumption of caffeine-containing beverages was permitted for four hours before the study.

On arrival at the laboratory, subjects were instructed to lie supine and to remain still throughout the study. A 19 gauge "butterfly" needle (Abbott Ltd) was inserted into a vein in the right arm for administration of drugs. An 18 gauge intravenous cannula (Jelco Ltd) was introduced into a forearm vein on the left arm for blood sampling.

MEASUREMENTS

Standard lead II of a surface electrocardiogram was continuously displayed on a cardiac monitor (Hewlett Packard Ltd). A precise heart rate was obtained at each phase in the study from the number of cardiac cycles recorded by the gamma camera during a five minute electrocardiogram gated left ventricular scintigram (see later).

Blood pressure, taken by the same investigator, was measured by auscultation in duplicate from the right arm every 60 seconds during left ventricular scintigraphy, using a standard mercury sphygmomanometer (Baumanometer Ltd). The systolic blood pressure used in the determination of each point in the systolic pressure/volume relation was thus the mean of 10 readings taken over a five minute period. (Blood pressure was also measured in the left arm at the beginning of the study and disparities between the two arms of >15 mmHg were not found.)

Left ventricular ejection fraction, end-systolic volume, and end-diastolic volume were determined by equilibrium radionuclide ventriculography (see data analysis).

The patient's own red cells were labelled with ^{99m} technetium (Tc) using the method of Smith and Richards.[11] Briefly, 4 ml venous blood were drawn into a heparinised syringe and incubated for five minutes with freeze-dried stannous citrate in a sterile

Table 1 *Clinical details of patients with previous myocardial infarction: symptomatic details and clinical class refer to time of study*

Subject	*Location of myocardial infarction*	*Coronary bypass surgery*	*Congestive heart failure*	*Angina*	*Arrhythmias*	*NYHA clinical class*	*Medications*
HC	Anterior	−	−	+	−	I	Nitrates
KB	Inferior	−	−	+	−	I	Nitrates
FC	Inferior	−	−	+	+	II	Frusemide, nitrates, propranolol
RS	Anterior	−	+	+	−	II	Quinidine, digoxin, nitrates
CD	Subendocardial	−	−	−	+	I	Quinidine
MW	Inferior	+	−	−	−	I	Digoxin
AH	Anterior	−	−	−	−	I	—
MR	Anterior	−	−	−	−	I	—
LG	Inferior	−	−	+	−	I	Nitrates
WW	Inferior	+	−	−	−	I	—
GM	Inferior	−	−	−	+	I	Quinidine, nitrates
HP	Anterior	+	−	−	−	I	—

evacuated glass tube. The tube was then centrifuged upside down for five minutes at 1300×*g* and the red cells carefully removed by needle aspiration through the rubber stopper.

Finally, the red cells were incubated in a sterile tube containing ^{99m}Tc (Nuclear Pharmacy Ltd) for a further five minutes before 1 ml red cell suspension, containing 15 to 20 mCi ^{99m}Tc, was reinjected intravenously to effect the blood pool label. Great care was taken to ensure a sterile technique and also to minimise damage to the red cells during the labelling procedure.

A single crystal gamma camera (Picker Dyna-Mo) fitted with a parallel hole, general purpose collimator, was then positioned over the subject's chest wall in a 45° left anterior oblique position, with 5 to 10° caudal tilt. The camera position was then further adjusted if necessary so that the image of the left ventricle was clearly separated from that of the right ventricle and the left atrium. Thereafter, the camera position remained unchanged.

PROCEDURE

After the subjects were in a basal haemodynamic state, a five minute equilibrium left ventricular scintigram, gated from a modified V5 electrocardiographic lead, was performed. Blood pressure was measured in duplicate each minute. At the mid-point of the scintigraphic acquisition, a 10 ml venous sample was drawn, from which 4 ml was pipetted for later gamma counting.

Then, 1 mg atropine sulphate (Abbott Ltd) was injected intravenously over five minutes. This was done to minimise the baroreflex mediated bradycardia that accompanies the infusion of pressor agents such as phenylephrine. After a further 10 minutes, left ventricular scintigraphy, blood sampling, and blood pressure measurements were repeated.

Next, an 80 μg/ml solution of phenylephrine hydrochloride (Winthrop Ltd) in normal saline was infused by means of a variable delivery rate pump (Ivac Ltd). The infusion was started at 80 μg/minute and titrated to produce target increments in systolic blood pressure of 15, 30, and 45 mmHg. When each target level of systolic blood pressure had been reached, it was held stable for five minutes while left ventricular scintigraphy was repeated. The heart rate was maintained within six beats per minute of that achieved after atropine by supplementary intravenous injections of atropine (0·1 to 0·3 mg) when necessary. In four patients with coronary artery disease, only two increments of phenylephrine were used because of the initial low ejection fraction.

DATA ANALYSIS

Equilibrium radionuclide studies were processed using a "Muga Cart" on-line computer (Medical Data Systems Ltd). Data recorded from each cardiac cycle during the five minutes of acquisition were divided into 28 equal time frames and integrated to construct a composite cardiac cycle. A rectangular region of interest was then placed around the composite left ventricular image, and an edge detection programme (Mug-O) used to define the boundary of the left ventricle throughout the cardiac cycle. (The edge detection algorithm utilises both absolute count rates and second derivatives of the count rate change in each time frame.) Background counts were automatically subtracted from the left ventricular region of interest to correct for non-cardiac activity. The five minute count rate exceeded 5000 in the left ventricular region of interest at end-diastole in all studies. Thus, a background corrected time-activity curve from the left ventricle was obtained, from which ejection fraction was calculated using the following equation:

$$\text{Ejection fraction} = \frac{(\text{end-diastolic counts}) - (\text{end-systolic counts})}{(\text{end-diastolic counts})}$$

Left ventricular end-diastolic volume was calculated by the method of Slutsky *et al.*[12] Left ventricular counts at end-diastole, corrected for frame time and the number of cardiac cycles processed, were divided by counts from whole blood drawn at the mid-point of each study, corrected for background activity, elapsed time, and radioactive decay.

Thus:

$$\left[\frac{\dfrac{(\text{end-diastolic counts})}{\text{cycles processed}} \times \dfrac{0{\cdot}04}{\text{time/frame}}}{\left(\begin{matrix}\text{Whole blood} \\ \text{counts}\end{matrix} - \begin{matrix}\text{Background} \\ \text{activity}\end{matrix}\right) \times \begin{matrix}\text{e} \cdot 115\text{x hours} \\ \text{elapsed}\end{matrix}}\right] \times 10^3$$

$$= \underline{\text{Arbitrary end-diastolic volume units.}}$$

Using a least squares linear regression derived from previous comparisons between radionuclide and contrast ventriculography at this institution,[13] end-diastolic volume was calculated as:

$$\text{EDV} = \frac{\left(\begin{matrix}\text{Arbitrary end-diastolic} \\ \text{volume units}\end{matrix}\right) - 0{\cdot}53}{0{\cdot}51} \text{ ml}$$

Using this determination of end-diastolic volume, stroke volume (SV) was calculated as:

$$\text{SV} = \text{EF} \times \text{EDV ml}$$

and, finally, ESV was calculated as:

$$\text{ESV} = \text{EDV} - \text{SV ml}$$

All ventricular volumes were reported as volume indices, that is ml/m^2 body surface area. The reproducibility of this technique has been validatd in our own and other laboratories. The reproducibility over time of end-diastolic volume and ejection fraction using this method was ±7·5 ml and ±3%, respectively.[14 15] Inter- and intra- observer variability have both been found to be approximately 4%.[15]

Individual plots were then constructed using three (n=8), four (n=12), or five (n=4) points to define the relation between the mean value of systolic blood pressure during a five minute scintigram and the calculated end-systolic volume index, over a physiological range of blood pressure.

Data were used only if heart rates during the various steps of phenylephrine infusion were successfully maintained within six beats a minute of the initial post-atropine value. Thus, the resting (pre-atropine) data were not included in these plots.

STATISTICAL ANALYSIS

Statistical comparisons within groups were performed using Wilcoxon's signed rank test and between groups using Wilcoxon's rank sum test. Regression analysis of paired data was performed on a Hewlett Packard model 9830A computer using a program which generated equations for the lines which best described these relations. All data are presented as the mean±1 standard deviation from the mean, except where otherwise stated.

Results

(1) HAEMODYNAMIC CHANGES AND COMPARATIVE EFFECTS ON P/V RATIO AND EJECTION FRACTION

At rest

The haemodynamic status of the 12 normal subjects and the 12 patients with coronary artery disease is shown in Table 2. Blood pressure and heart rate were similar in the two groups, the major difference being a larger end-systolic volume in the patients with coronary disease (50±24 ml/m² compared with 22±7 ml/m² in the normals, p<0·01).

While the mean P/V ratio was significantly lower in the patients with coronary disease than the normal subjects (2·79±1·00 mmHg/ml per m² compared with 6·23±2·47 mmHg/ml per m², p<0·01), it was not significantly better than the ejection fraction in the identification of individual patients with left ventricular dysfunction caused by coronary artery disease (Fig. 1).

After atropine

The response to 1 mg intravenous atropine is shown in the left hand panels of Tables 3 and 4 for normal subjects and patients with coronary artery disease, respectively. Heart rate rose by 20 to 25 beats a minute and diastolic blood pressure rose by 5 to 8 mmHg in each group. The P/V ratio was significantly increased by atropine in the normal subjects (from 6·23±2·47 to 7·28±2·7 mmHg/ml per m², p<0·01) but did not rise significantly in the patients with coronary artery disease (from 2·79±1·00 to 3·28±1·66 mmHg/ml per m²).

By contrast, the ejection fraction showed a non-significant decline after atropine in both groups. In the patients with coronary disease, stroke volume fell significantly (from 50±24 to 32±12 ml/m², p<0·01) but was maintained in the control group (53±13 ml/m² at rest, 46±18 ml/m² after atropine −NS).

Fig. 2 is a plot of the relation between the P/V ratio and the ejection fraction after atropine administration. The relation is best described by the exponential equation $y=0{\cdot}82\times e^{0{\cdot}3X}$, as illustrated. Note that most of the normal subjects lie on the steep part of the curve, where ejection fraction is relatively insensitive to changes in the P/V ratio.

Table 2 *Resting haemodynamic data in normal subjects and patients with coronary disease*

Normal subjects								*Coronary disease patients*							
Subject	*BP (mmHg)*	*HR (bpm)*	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*P/V (mmHg/ml per m²)*	*EF (%)*	*Subject*	*BP (mmHg)*	*HR (bpm)*	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*P/V (mmHg/ml per m²)*	*EF (%)*
WC	117/69	67	84	23	61	5·09	73	HC	106/65	61	81	45	36	2·36	44
DJ	112/61	71	90	24	66	4·67	73	KB	136/68	80	89	45	44	3·02	49
ML	117/71	58	99	36	63	3·25	64	FC	100/65	46	68	24	44	4·17	65
RC	120/70	70	75	22	53	5·45	70	RS	105/70	56	121	94	27	1·12	22
MB	120/79	54	72	21	51	5·71	71	CD	108/62	88	42	29	13	3·72	30
GM	128/70	58	62	15	47	8·53	76	MW	122/84	70	77	40	37	3·05	48
PW	127/79	52	92	26	66	4·88	71	AH	132/80	55	68	42	26	3·14	39
DE	118/75	72	50	11	39	10·73	78	MR	117/60	71	96	56	40	2·09	41
WE	128/69	68	58	24	34	5·33	59	LG	122/71	54	94	32	62	3·81	66
WM	110/82	93	56	26	30	4·23	53	WW	135/75	53	129	61	68	2·21	53
SS	130/75	71	72	12	60	10·83	83	GM	114/72	53	76	32	44	3·56	58
HR	127/74	82	85	21	64	6·05	76	HP	115/75	97	126	98	28	1·17	22
M	121/73	68	75	22	53	6·23	71	M	118/71	65	89	50	39	2·79	45
SD	± 7/6	±12	±16	± 7	±13	± 2·47	± 8	SD	± 12/7	±16	± 26	±24	±15	±1·00	±15

BP, blood pressure; HR, heart rate; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; SVI, stroke volume index; P/V, peak systolic blood pressure/end-systolic volume index ratio; EF, ejection fraction.

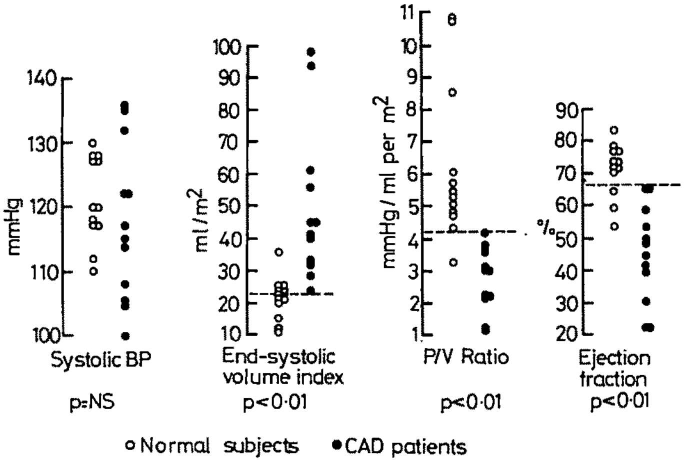

Fig. 1 *Comparison of resting values of systolic blood pressure, end-systolic volume, P/V ratio, and ejection fraction in normal subjects and patients with coronary artery disease (CAD). The dotted lines denote the values that best discriminate between the two groups.*

During phenylephrine

The maximum haemodynamic respone to the pressor effects of phenylephrine are shown in the right hand panels of Tables 3 and 4 for normal subjects and patients with coronary disease, respectively. Mean systolic blood pressure was similarly raised (42 and 39 mmHg) in both groups, and in no subject was heart rate permitted to fall by >6 beats/minute from the post-atropine value. The P/V ratio fell in both groups but was only significantly reduced in the normal subjects (from 7·28±2·27 to 5·87±1·40 mmHg/ml per m^2, $p<0\cdot01$).

Mean ejection fraction also fell in both groups during phenylephrine though again this was only

Table 3 *Haemodynamic data in normal subjects (left) 10 minutes after 1 mg atropine given intravenously and (right) during maximum infusion rate of phenylephrine*

After atropine								*During maximum phenylephrine infusion*						
Subject	*BP (mmHg)*	*HR (bpm)*	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*P/V (mmHg/ml per m²)*	*EF (%)*	*BP (mmHg)*	*HR (bpm)*	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*P/V (mmHg/ml per m²)*	*EF (%)*
WC	130/83	91	50	17	33	7·65	66	170/124	96	82	31	51	5·48	62
DJ	111/67	92	97	18	79	6·17	81	163/109	93	103	29	74	5·62	72
ML	117/77	88	90	34	56	3·44	62	158/115	95	105	47	58	3·36	55
RC	120/78	98	55	18	37	6·67	68	185/125	94	88	43	45	4·30	49
MB	127/81	87	59	17	42	7·47	71	172/117	89	80	25	55	6·88	69
GM	132/85	84	52	14	38	9·43	73	179/128	84	85	24	61	7·46	72
PW	134/85	85	96	23	73	5·83	76	165/98	79	101	33	68	5·00	67
DE	123/78	86	49	11	38	11·18	78	155/104	86	65	18	47	8·61	72
WE	126/80	94	40	19	21	6·63	53	165/109	92	65	30	35	5·50	53
WM	120/85	99	50	22	28	5·45	56	150/108	96	60	30	30	5·33	50
SS	132/70	97	69	12	57	11·00	82	178/87	95	102	25	77	7·12	75
HR	128/68	94	72	20	52	6·40	72	163/90	98	94	28	53	5·82	66
Mean	125*/78*	91**	65*	19**	46	7·28**	70	167**/110**	91	86**	30**	55*	5·87**	64**
SD	±7/7	±5	±20	±6	±18	±2·27	±9	±10/13	±6	±16	±8	±14	±1·4	±9

*p<0·05, **p<0·01 } compared with resting values.

*p<0·05, **p<0·01 } compared with post-atropine values.

For key to abbreviations see Table 2.

Table 4 *Haemodynamic data in coronary disease patients (left) 10 minutes after 1 mg atropine given intravenously and (right) during maximum rate of infusion of phenylephrine*

	After atropine							*During maximum phenylephrine infusion*						
Subject	*BP (mmHg)*	*HR (bpm)*	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*P/V (mmHg/ml per m²)*	*EF (%)*	*BP (mmHg)*	*HR (bpm)*	*EDVI (ml/m²)*	*ESVI (ml/m²)*	*SVI (ml/m²)*	*P/V (mmHg/ml per m²)*	*EF (%)*
HC	104/75	82	75	45	30	2·31	40	145/100	86	93	61	32	2·38	35
KB	116/70	96	66	29	37	4·00	56	157/91	93	79	47	32	3·34	41
FC	110/80	75	74	41	33	2·68	45	180/130	80	146	86	60	2·09	41
RS	104/76	79	128	104	24	1·00	19	137/95	81	160	118	42	1·16	26
CD	123/65	101	45	32	13	3·84	29	143/100	99	48	40	8	3·57	17
MW	124/101	85	55	28	27	4·42	49	165/110	80	76	42	34	3·93	45
AH	140/92	82	55	36	19	3·89	35	190/110	79	81	54	27	3·52	32
MR	109/53	93	85	54	31	2·02	36	161/93	91	108	75	33	2·15	30
LG	140/80	81	61	21	40	6·67	65	160/108	76	79	27	52	5·93	66
WW	154/90	76	128	65	63	2·37	50	185/106	72	137	77	60	2·40	44
GM	126/86	77	59	25	34	5·04	58	160/105	75	64	35	29	4·57	45
HP	116/80	108	130	101	29	1·15	22	150/110	106	151	121	30	1·24	20
M	122/79*	86**	80	48	32*	3·28	42	161**/105**	85	102**	65**	37	3·02	37
SD	±16/13	±11	±31	±28	±12	±1·66	±14	±17/10	±10	±38	±31	±15	±1·39	±13

*p<0·05, **p<0·01 } compared with resting values.

*p<0·05, **p<0·01 } compared with post-atropine values.

For key to abbreviations see Table 2.

significant in the normal subjects (from 70±9 to 64±9%, $p<0{\cdot}01$). Thus, the P/V ratio and the ejection fraction appeared to be similarly afterload-dependent in both groups studied.

(2) LINEARITY AND SLOPE OF PEAK SYSTOLIC PRESSURE/END-SYSTOLIC VOLUME RELATION

The relation between peak systolic pressure and end-systolic volume was found to be linear over a physiological range of blood pressure ($r \geq 0{\cdot}91$) in all 24 subjects studied. The slopes of these lines were significantly steeper in normal subjects than in the patients with coronary artery disease (3·9±0·9 mmHg/ml per m² compared with 2·5±0·6 mmHg/ml per m², $p<0{\cdot}05$) though there was some overlap of individual values between the two groups (Fig. 3). Ten of 12 normal subjects, however, but only four of 12 patients with coronary disease had a P/V slope >2·7 mmHg/ml per m².

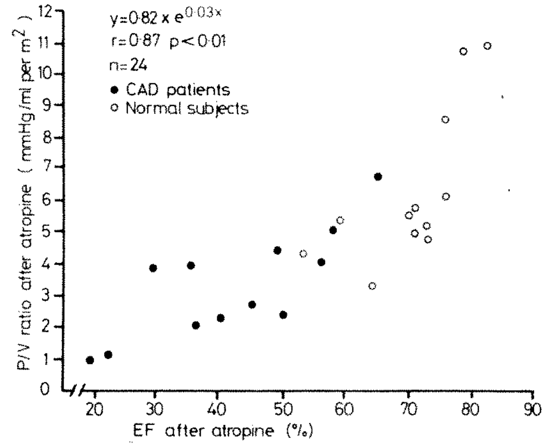

Fig. 2 *Plot showing the exponential relation between the P/V ratio and the ejection fraction (EF) determined simultaneously (in this case after atropine).*

The P/V slope correlated exponentially with the ejection fraction determined at the same heart rate (that is after atropine), as shown in Fig. 4. Thus, as with the P/V ratio, most of the normal subjects fell on the steep part of the curve, where the ejection fraction is relatively insensitive to changes in the P/V slope.

The observed intercept of the P/V slope on the volume axis was not significantly different between the two groups (see Table 5 for individual linear regression data).

(3) THEORETICAL VALUE FOR END-SYSTOLIC VOLUME AT ZERO SYSTOLIC PRESSURE—V_0

V_0 was calculated as $-b/a$ where a is the P/V slope and b is the observed intercept on the volume axis. Mean V_0 was -16 ± 10 ml/m² in the normal subjects and -4 ± 25 ml/m² in the coronary artery disease group (NS). No significant correlation was found between V_0 and ejection fraction overall, though there appeared to be a trend towards an inverse relation with values of less than 50% for ejection fraction (Fig. 5).

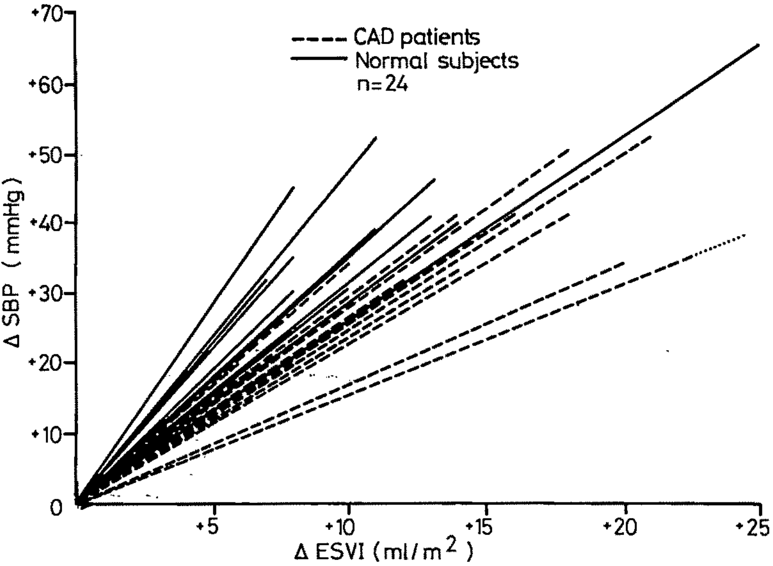

Fig. 3 *Individual plots showing the linear relation between the increase in systolic blood pressure and the resultant rise in end-systolic volume. The slope of these lines in the patients with coronary artery disease tends to be less steep than in normal subjects, but there is some overlap of the two groups.*

Table 5 *Characteristics of peak systolic pressure/end-systolic volume relation over physiological range of systolic blood pressure*

Normal subjects					*Coronary disease patients*				
Subject	*r*	*Slope*	*Intercept*	V_0	*Subject*	*r*	*Slope*	*Intercept*	V_0
WC	0·97	2·7	+88	−33	HC	0·98	2·5	−7	+3
DJ	0·98	5·0	+19	−4	KB	0·93	2·8	+63	−23
ML	0·99	3·3	+6	−2	FC	0·99	1·6	+46	−29
RC	0·99	2·6	+73	−28	RS	0·93	2·1	−105	+50
MB	0·98	5·2	+39	−8	CD	0·96	2·0	+59	−30
GM	0·95	4·8	+68	−14	MW	0·94	2·7	+57	−21
PW	0·99	3·1	+63	−20	AH	0·99	2·6	+50	−20
DE	0·99	4·6	+72	−16	MR	0·97	2·5	−28	+11
WE	0·91	3·3	+53	−16	LG	0·98	3·8	+61	−16
WM	0·99	3·8	+40	−11	WW	0·99	2·8	−25	+9
SS	0·96	3·5	+96	−27	GM	0·99	3·3	+36	−11
HR	0·97	4·4	+45	−10	HP	0·98	1·6	−51	+32
M	0·97	3·9	+55	−16		0·97	2·5*	13	−4
SD	±0·02	±0·9	±27	±10		±0·02	±0·6	±55	±25

*$p<0·01$ compared with normal subjects. r, linear coefficient of correlation between systolic BP and end-systolic volume over a physiological range of BP, that is y mmHg=ax+b ml/m² where a=slope, b=intercept, and $V_0=-b/a$ (theoretical end-systolic volume index at zero pressure).

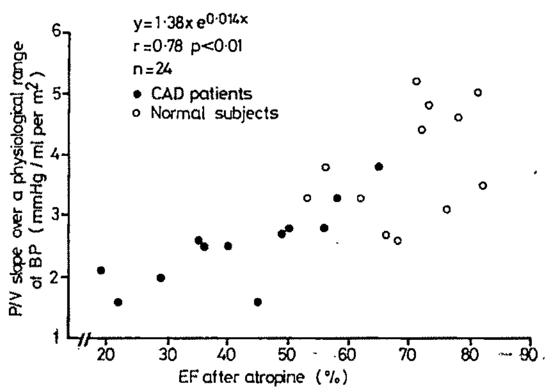

Fig. 4 *Plot showing the exponential relation between the P/V slopes seen in Fig. 3 and the ejection fraction determined at the same heart rate, that is immediately after atropine.*

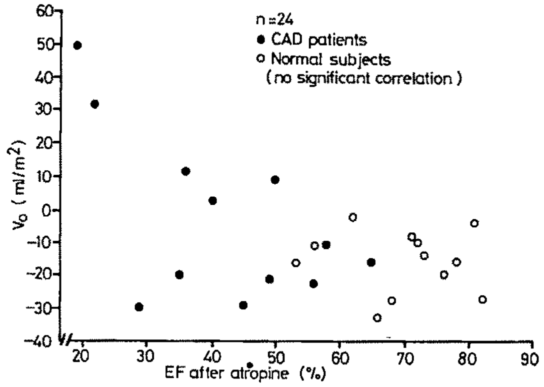

Fig. 5 *Plot of V_0 against ejection fraction (EF) determined at the same heart rate. Though no significant correlation was found overall, there was a trend towards an inverse correlation in patients whose post-atropine ejection fraction (EF) was <36%.*

Discussion

This study has confirmed the linearity of the peak systolic pressure/end-systolic volume relation in man at a constant inotropic state and over a physiological range of blood pressure. Previous studies using M-mode echocardiography[16] and contrast ventriculography[6] have also shown a linear relation but, unlike radionuclide ventriculography, both these methods are dependent on geometric assumptions about the shape of the left ventricle at end-systole, assumptions that may be particularly inappropriate in patients with previous myocardial infarction.

The slope of this relation has been shown in previous clinical and experimental studies to be an index of inotropic state.[2 4 16]

We found an exponential relation between the P/V slope and the ejection fraction, confirming the findings of Mehmel *et al.*[6] Most normal subjects fell on the steep part of the curve (see Fig. 4) suggesting that the P/V slope might be more sensitive to changes in inotropic state than the ejection fraction, at least in such normal subjects.

Although the mean P/V slope was steeper in the normal subjects than in those with coronary disease, there was considerable overlap between the two groups, presumably because the resting contractile state of the left ventricle is not invariably depressed after myocardial infarction.

The ejection fraction is commonly used in clinical practice as a measure of the contractile state of the left ventricle, but it is also influenced by changes in heart rate, preload, and afterloading conditions. Thus, when preload is decreased or afterload increased, the ejection fraction is depressed even if the inotropic state of the left ventricle is constant. Despite this limitation, the ejection fraction is widely used to detect, quantify, and prognosticate upon left ventricular dysfunction in patients with coronary artery disease.[17-19]

The P/V slope, however, being linearly afterload dependent and virtually unaffected by preload, may more accurately reflect the inotropic state of the left ventricle than the ejection fraction under circumstances where both cardiac loading conditions and inotropic state are changing. Indeed, the P/V relation is now being used to evaluate cardiovascular drug effects in man.[10 20]

By contrast, the extrapolated value of end-systolic volume at zero pressure (V_0) did not correlate significantly with the ejection fraction in our study, nor was it significantly different in subjects with and without left ventricular dysfunction caused by coronary artery disease. This is in contrast to the findings of Grossman *et al.*,[4] who observed a significantly higher value for V_0 in patients with a depressed ejection fraction than those with a normal ejection fraction, as assessed by contrast ventriculography.

Only the subgroup of five patients with severely impaired myocardial performance in Grossman's study (mean ejection fraction 24%), however, had a significantly higher value of V_0, and this tendency was observed in the five patients in our study with an ejection fraction <36% (see Fig. 5). In addition, there were no normal subjects in Grossman's study, and those with normal ejection fractions had evidence of systolic volume overload (mean end-systolic volume was 51 ml/m^2). Thus, it appears that V_0 is not a sensitive index of myocardial performance in normal subjects and seems to be consistently raised only when both myocardial contractility is severely impaired and end-systolic volume is greatly enlarged.

The P/V ratio was of similar sensitivity to the ejection fraction in the detection of patients with left ventricular dysfunction caused by coronary artery disease, at rest and after each of the pharmacological interventions. One interesting difference was in the response to atropine in the normal subjects. The P/V ratio rose in all 12 subjects after atropine, whereas the ejection fraction only rose in four subjects. Since it is now established that an increase in heart rate *per se* constitutes a positive inotropic stimulus in man,[21] these findings further support the increased sensitivity of the systolic P/V relation over the ejection fraction as an index of the prevailing inotropic state.

Increasing afterload on the left ventricle with phenylephrine led to a similar dose-dependent decline in both the P/V ratio and the ejection fraction—both more pronounced in the normal subjects than in the patients with coronary artery disease. It was assumed for the purposes of this study that phenylephrine infusion in the presence of an atropine-induced vagolysis had no reflex effects upon the inotropic state of the left ventricle. No patient complained of chest pain or had electrocardiographic abnormalities during the phenylephrine infusion, but nearly all subjects had a transient throbbing headache at the highest dose.

Isometric and dynamic exercise generally increase the sensitivity of indices of myocardial performance for differentiating normal subjects from those with left ventricular dysfunction caused by coronary artery disease. This has proved to be the case with studies using the systolic pressure/volume relation.[7 8] The response of both blood pressure and heart rate to any given level of exercise, however, may vary widely, both within and between subjects. We felt that pharmacological afterload stress, with control of the systolic blood pressure and heart rate, might further increase the sensitivity of this index for detecting minor degrees of left ventricular dysfunction caused by coronary artery disease. The fact that no such increase in sensitivity was seen may be because our study did not incorporate a positive inotropic stimulus such as that which occurs with exercise, and a study using isoprenaline under similar conditions is in progress.

One potential limitation on the interpretation of our findings is the younger mean age of the normal subjects. We are not aware of any studies that show an effect of age *per se* on ejection phase indices of myocardial contractility. Aortic impedance may increase with age and it is thus possible that this would further depress the ejection fraction and the P/V ratio in the coronary disease group.[22]

In conclusion, this study has evaluated the clinical utility of the peak systolic pressure end-systolic volume relation in normal subjects and patients with coronary artery disease. While neither the P/V ratio nor the P/V slope appeared to be significantly better than the ejection fraction in the detection of left ventricular dysfunction resulting from coronary artery disease, the P/V ratio may more closely reflect the prevailing inotropic state of the left ventricle. Unlike both the P/V ratio and the ejection fraction, the P/V slope is independent of afterload and may therefore have special utility in the evaluation of cardiovascular drug effects in man.

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Systolic closure of aortic valve in patients with prosthetic mitral valves

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SUMMARY Systolic closure of the aortic valve was found in 10 of 36 patients who underwent mitral valve replacement. Eight patients had early systolic closure, and two had mid-systolic closure.

The left ventricular outflow tract dimension on M-mode and two dimensional echocardiograms, left ventricular posterior wall and septal thickness, left ventricular dimensions in systole and diastole, aortic valve opening, and mitral to aortic valve distance were not significantly different between patients with and without systolic closure of the aortic valve. Two of the 10 patients with systolic aortic valve closure were catheterised and in neither was there a gradient between the left ventricle and the aorta. The two patients with mid-systolic closure, however, were the patients who had the narrowest left ventricular outflow tract which could cause significant distortion of blood flow. Systolic closure of the aortic valve in patients with mitral valve replacement is probably not caused by left ventricular outflow tract obstruction, though abnormalities in laminar flow from the left ventricular outflow tract may be involved.

Mid-systolic partial closure of the aortic valve is one of the main echocardiographic features of hypertrophic cardiomyopathy,[1–3] and has been reported in cases of ruptured aneurysm of the right coronary sinus of Valsalva,[4] mitral regurgitation,[5] and ventricular septal defect.[5] Early partial systolic closure of the aortic valve is one of the echocardiographic hallmarks of discrete subaortic stenosis,[6 7] and has been described in a patient with parachute accessory mitral valve leaflet.[8]

We have noted the occurrence of early and mid-systolic closure of the aortic valve in patients with a mitral valve prosthesis. We report a study of this phenomenon aimed at finding its prevalence, clinical significance, and aetiology.

Subjects and methods

Thirty-six consecutive patients who underwent mitral valve replacement six months to 12 years (average 4·7 years) before the start of this study were studied prospectively. Twelve were male and 24 female; their ages ranged from 15 to 72 years (average 50·4 years). Twenty-three had a Starr-Edwards mitral prosthesis, and 13 had a Björk-Shiley prosthesis. The reasons for mitral valve replacement were pure mitral stenosis in nine, pure mitral regurgitation in nine, and combined mitral valve disease in 18 patients. In addition, seven had aortic regurgitation, four tricuspid regurgitation (for which one had a tricuspid valve replacement), and three coronary artery disease, with aortocoronary bypass surgery in one patient.

ECHOCARDIOGRAPHY

M-mode and two dimensional echocardiograms were recorded using the Aloka model SSD-1105-E echocardiograph. M-mode echocardiograms were obtained with a 2·25 MHz transducer focused at 5 cm, and two dimensional echocardiograms with a handy scanner mechanical sector model ASV-25V, with a 90° sector with 5 to 30 c/s.

Left ventricular posterior wall and interventricular septal thickness, left ventricular systolic and diastolic dimensions, and the extent of aortic valve opening were recorded on the M-mode echocardiograms using standard methods.[9] Two aortic valve cusps (right and non-coronary) were clearly recorded in all patients. Early systolic left ventricular outflow tract dimension was obtained on the M-mode by measuring the sagittal distance between the left side of the interventricular septum and the echo of the leading edge of the mitral sewing ring (defined as the first continuous line recorded from the prosthesis) at the onset of systole (Fig. 1). Early systolic left ventricular outflow tract

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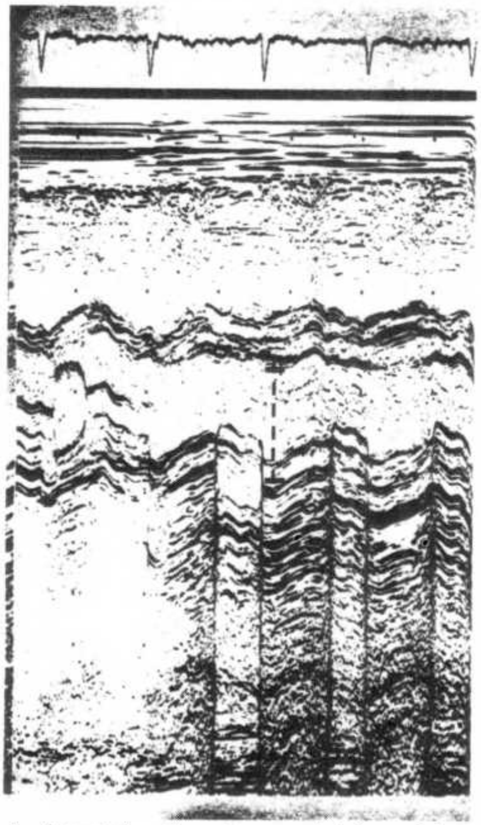

Fig. 1 *A sweep from the aortic root to the left ventricular outflow tract. The whole dimension is depicted by the vertical broken line.*

dimension was obtained from the two dimensional echocardiogram by measuring the minimal distance from the left side of the interventricular septum to the sewing ring of the prosthesis (Fig. 2). In addition, we measured the distance between the aortic valve and the leading edge of the prosthetic valve in mid-diastole (Fig. 3).

Early systolic closure of the aortic valve was defined as a sharp movement towards the centre of the aorta by one or both visible cusps (right and/or non-coronary) immediately after the maximal opening of the aortic valve. Mid-systolic closure was defined using the same criteria in mid-systole.

CARDIAC CATHETERISATION

Two patients had undergone left heart catheterisation. Resting pressures were recorded by slow withdrawal of the catheter from the left ventricular apex through the left ventricular cavity to the aorta. The angiographic studies included left ventriculography and coronary angiography.

STATISTICS

The probability value (P) was calculated by Student's t test and the Fisher two by two exact probability test.

Results

Systolic partial closure of the aortic valve was noted in 10 patients (group A), who could be divided into two subgroups. Group A1: two patients with mid-systolic closure of the aortic valve both had Starr-Edwards prosthetic valves (Fig. 4). Group A2: eight patients with early systolic closure of the aortic valve (Fig. 5) of whom four had Starr-Edwards and four had Björk-Shiley valves.

The remaining 26 patients had normal opening of the aortic valve (group B). There was no statistically significant difference between groups A and B regarding the interventricular septal thickness, left ventricular systolic and diastolic dimensions, interventricular septum/posterior wall thickness ratio, aortic valve opening, the dimensions of the left ventricular outflow tract on M-mode and two dimensional echocardiograms, and the aortic to mitral valve distance on the two dimensional echogram (Table).

It should be emphasised, however, that the two patients with mid-systolic closure of the aortic valve (A1) were distinct in having the narrowest left ventricular outflow tract dimensions on both M-mode (0·8 cm and 0·9 cm, respectively) and two dimensional echogram (0·5 cm each). In addition, both had a short mitral to aortic valve distance (0·5 and 0·9 cm).

Systolic fluttering of the aortic valve was found in nine patients in group A (90%) and 10 patients in group B (38·5%) (not significant on Fisher's test). Two patients, one in group A1 and the other in group A2, underwent cardiac catheterisation. No pressure gradients were found between the body of the left ventricle, left ventricular outflow tract, and the aorta. The patient in group A1 was catheterised because of a systolic ejection type murmur associated with mid-systolic closure of the aortic valve on echocardiography, raising the suspicion of left ventricular outflow tract obstruction. The patient in group A2 was catheterised because of angina.

Discussion

The present study disclosed a high prevalence of systolic partial closure of the aortic valve in patients with prosthetic mitral valves. To the best of our knowledge this phenomenon has not been previously reported. The prevalence of systolic closure in patients with the Starr-Edwards prosthesis (6/23, 26%) and those with the Björk-Shiley prosthesis (4/13, 29%) was not statistically different ($p<0·05$).

Abnormal systolic closure of the aortic valve,

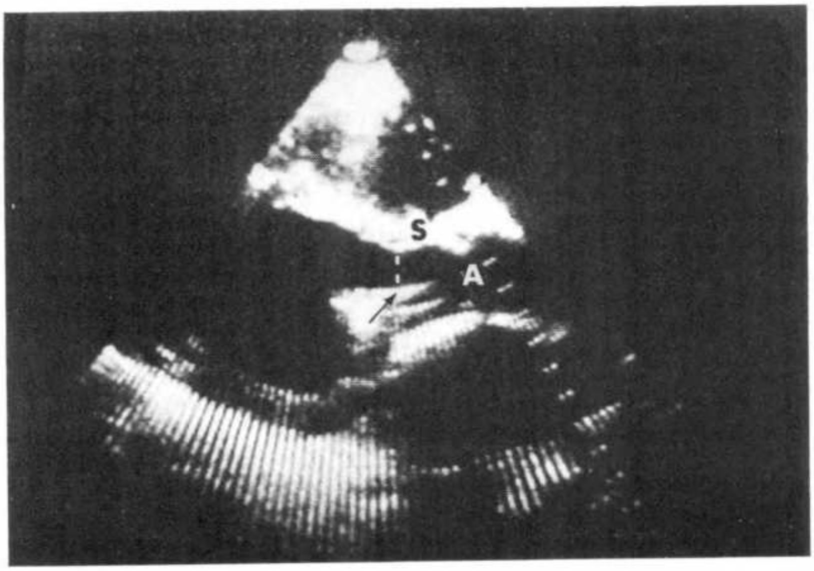

Fig. 2 *Two dimensional echocardiogram showing the sewing ring of the prosthetic mitral valve (arrow), the interventricular septum (S), and aorta (A) in early systole. The left ventricular outflow tract dimension is depicted by the vertical broken line.*

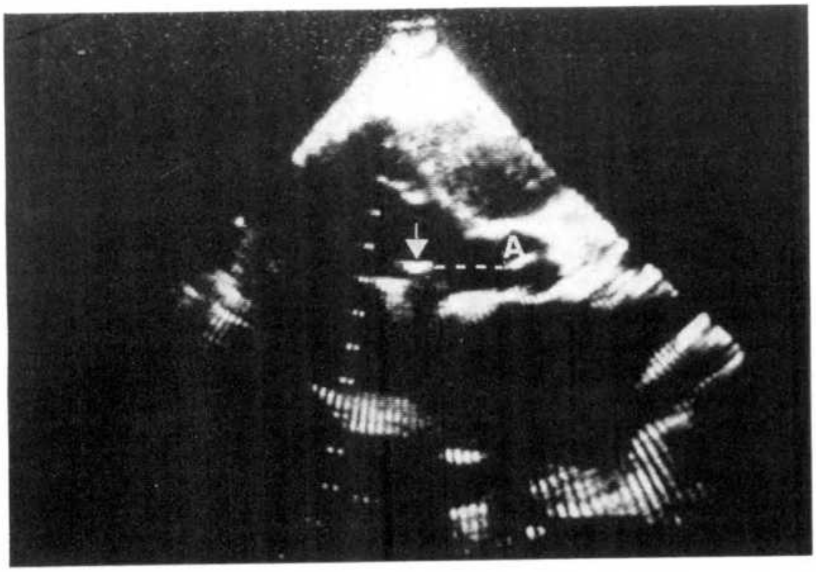

Fig. 3 *Two dimensional echocardiogram showing the prosthetic mitral valve (arrow), and the aortic valve (A) in mid-diastole. The distance between the mitral and aortic valves is depicted by the horizontal broken line.*

though recorded in different clinical situations,[4 5 10 11] has been investigated only in the setting of discrete subaortic stenosis and hypertrophic obstructive cardiomyopathy.[1 12] The incidence of this phenomenon in discrete subaortic stenosis is high,[12 13] but its mechanism has not been clearly defined. It could be caused by the fixed left ventricular outflow tract obstruction creating a jet of turbulent blood that alters the normal motion of the aortic valve cusps.[7 14] It should be emphasised that the aortic valve motion in our patients with early closure differs from that usually seen in discrete subaortic stenosis. In the latter situation the closure is generally abrupt and pronounced and the cusps remain in this semi-open position throughout systole.[4 5] Contrary to this pattern, in our patients closure is less distinct and the aortic valve cusps reopen and remain in a fully open position until end-systole. This difference implies some diversity in mechanisms. Our patients differ from patients with discrete subaortic stenosis by the lack of left ventricular outflow tract obstruction. There were no significant differences between groups A and B

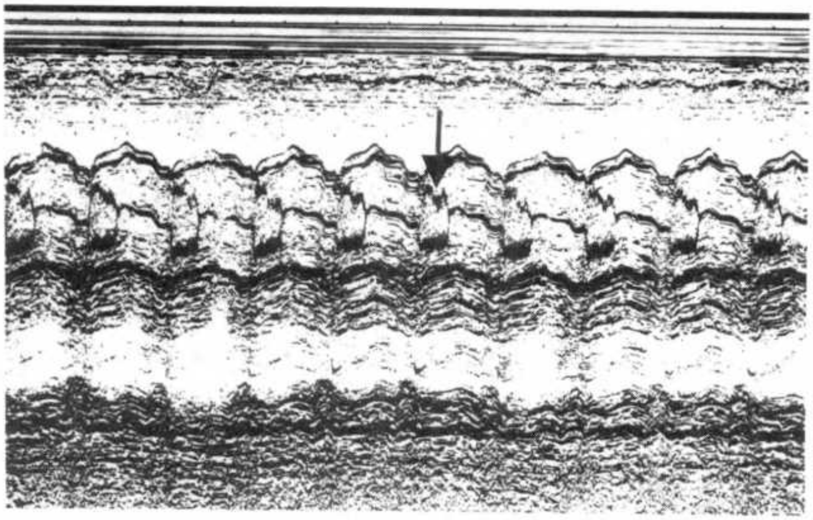

Fig. 4 *Mid-systolic closure of the aortic valve (arrow).*

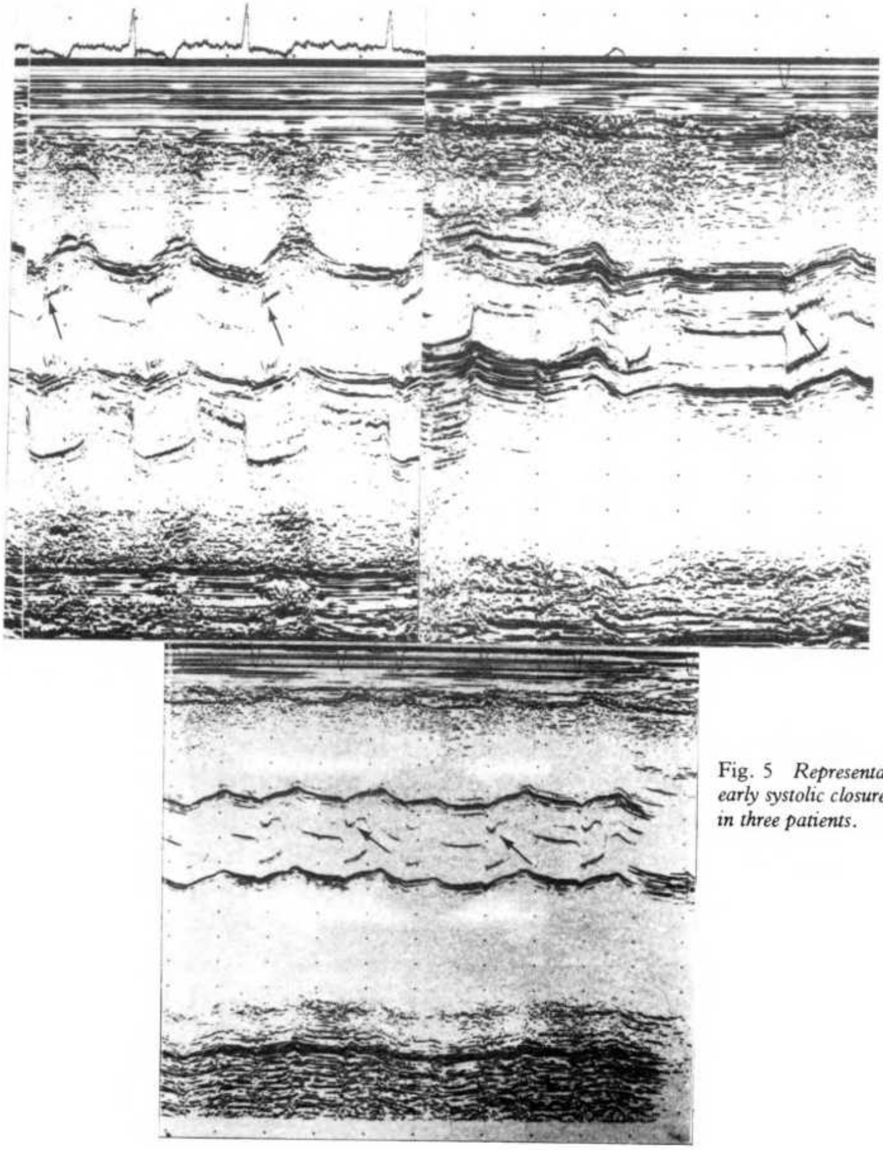

Fig. 5 *Representative echocardiograms of early systolic closure of the aortic valve (arrows) in three patients.*

Table *Comparison of echocardiographic variables in patients with and without systolic closure of aortic valve*

	Systolic closure (group A)	*Normal closure (group B)*
Left ventricular posterior wall thickness (cm)	0·98±0·12	0·96±0·09
Interventricular septal wall thickness (cm)	0·91±0·06	0·97±0·09
Left ventricular systolic dimension (cm)	3·46±0·7	3·74±1·15
Left ventricular diastolic dimension (cm)	5·16±0·5	5·28±1·12
Aortic valve opening (cm)	1·82±0·27	1·73±0·32
Left ventricular outflow tract dimension (M-mode) (cm)	2·32±1·07	2·09±0·53
Left ventricular outflow tract dimension (2 D) (cm)	1·46±0·79	1·74±0·61
Distance between mitral and aortic valves (2 D) (cm)	0·95±0·59	1·02±0·32

regarding left ventricular outflow tract dimensions at the onset of systole on both M-mode and two dimensional echocardiograms (Table). Moreover, the lack of pressure gradient between the left ventricle, left ventricular outflow tract, and aorta in the patient in group A2 further supports our view. One possible explanation involves the presence of the prosthesis in the left ventricular outflow tract root which might cause some anatomical distortion and abnormality of the blood flow in this region. Another mechanism could be an abrupt tilt of the prosthesis shortly after the closure of the poppet, thereby changing the blood flow pattern across the aortic valve.

Two patients (group A1) had mid-systolic closure similar to that of hypertrophic obstructive cardiomyopathy. The early closure in hypertrophic obstructive cardiomyopathy is postulated to be caused by mid-systolic left ventricular outflow tract obstruction resulting from the protruding interventricular septum on the one hand and the anterior systolic motion of the mitral valve on the other.[1 15–17] This finding in our patients gave rise to the suspicion of left ventricular outflow tract obstruction. Haemodynamic studies in one patient, however, disclosed no pressure gradient between the left ventricle, left ventricular outflow tract, and the aorta. Thus we must conclude that left ventricular outflow tract obstruction was not instrumental in causing mid-systolic closure in at least one of our patients. Nevertheless, the narrow left ventricular outflow tract combined with the distinctly short mitral to aortic valve distance could cause distortion of the blood flow in the left ventricular outflow tract and hence produce an abnormal motion pattern of the aortic valve. In addition, the high incidence of fluttering lends support to the hypothesis that prosthetic mitral valves in some way alter the laminar left ventricular outflow tract flow pattern.

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Morphometric investigations in mitral stenosis using two dimensional echocardiography

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SUMMARY A method is proposed for comparing the orifice size and the morphology of stenotic mitral valves, removed intact at the time of replacement, with the preoperative two dimensional echocardiographic cross-sections. The excised mitral valve apparatus is suspended on a specially constructed mounting. To avoid shrinkage the orifice is stabilised with an airfilled balloon. A radiograph is taken directing the *x*-ray beam perpendicular to the valve orifice.

In 40 of 51 patients this method provided the means of relating the echocardiographic cross-sections to the morphology of the valve. Planimetry of the valve area compared favourably with the postoperatively determined orifice size. Agreement was found in 34 of 40 patients in orifice shape between preoperative echocardiograms and *x*-rays of the excised valve. The relation between intraoperative estimation of size of the valve, using dilators with known diameters, and the postoperative results was less favourable.

Areas of calcification were identified on echocardiography as dense conglomerate echoes. In 30 patients (75%) the localisation of calcium deposits and in 67% the degree of calcification was in agreement with the *x*-rays of the valve taken after operation.

In addition to determination of the area, two dimensional echocardiography allows detailed studies of the stenotic valves, and is of particular importance for planning operative treatment.

The limitations of M-mode echocardiography in predicting the severity of mitral valve stenosis are well known.[1 2] In contrast, with two dimensional echocardiography in short axis planes it is possible to image the total circumference of the stenosed valve orifice. The valve area can then be calculated by means of planimetry.[3] Several studies have correlated those measurements with the Gorlin-derived valve area.[4–6]

In addition, Henry *et al.*[3] found a close correlation between cross-sectional echocardiography and intraoperative measurement. In 13 of 14 patients with mitral valve disease the orifice area measured from two dimensional images was within 0·3 cm^2 of the orifice area measured directly at operation. But in these investigations the morphology of the mitral valve apparatus, obtained by both methods, had not been analysed in detail.

The purpose of this study was to assess the role of cross-sectional echocardiography in predicting the area and shape of the orifice as well as the grade and distribution of valve calcifications. Therefore a special method for morphometric analysis of stenosed valves removed during operation was proposed.

Subjects and methods

The study group consisted of 51 consecutive patients undergoing operation for mitral valve disease. There were 35 women and 16 men whose ages ranged from 36 to 69 years, mean 52 years.

Cardiac catheterisation was performed in each patient: 18 had pure mitral stenosis, and 33 had clinical and angiographic evidence of associated mild to moderate mitral regurgitation.

ECHOCARDIOGRAPHIC METHODS

All ultrasonic examinations were carried out using a commercially available phased array 80° sector scanner (Varian V3000, Varian Ass. Palo Alto, USA). This instrument has been previously described in detail.[7] The two dimensional echocardiographic investigations were performed using a method similar

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to that described by Henry *et al.*[3] The transducer was placed in the left parasternal region, usually in the third, fourth, or fifth intercostal space. The sector scan image was initially orientated parallel to the long axis of the left ventricle in order to visualise the anterior and posterior mitral leaflets with their chordal and papillary muscle attachments. The transducer was then rotated 90° clockwise to obtain a short axis view of the left ventricle. From the transducer position a sweep was performed by slowly angling the image plane from the aorta to the apex. Thus the stenotic mitral valve orifice, forming the apex of the mitral valve funnel, could be directly imaged. Care was taken to adjust the instrument to an optimal level so that continuous echoes around the circumference of the orifice could be recorded.

The cross-sectional images were recorded on a ½ inch videotape system for later playback and review (Sanyo VTC 3000, Sanyo USA). The illustrations presented in this article are 35 mm photographs of single frame images from the videotape.

INTRA- AND POSTOPERATIVE ASSESSMENT

During operation an estimate of the dimensions of the mitral valve orifice was made using Hegar dilators with known diameters. The circle area (πr^2) was calculated.

In patients where valve replacement was thought to be necessary the intact mitral valve including the chordae and the tips of the papillary muscles was excised. The valve was carefully examined by palpation and was subsequently suspended on a specially constructed holding. To avoid shrinkage the orifice was stabilised with an airfilled balloon of known pressure. The balloon pressure was individually adjusted to the rigidity of the valve and did not exceed 25 mmHg. Then a radiograph was taken, directing the *x*-ray beam perpendicular to the mitral valve orifice. A radio-opaque scale was simultaneously filmed for later quantification (Fig. 1).

Thus, the shape and the area of the orifice and the amount of calcium around the circumference could be judged by a technique similar to cross-sectional echocardiography.

DATA ANALYSIS

The two dimensional echocardiograms were interpreted in a double-blind fashion and without knowledge of the later radiographic findings of the excised mitral valve.

The orifice area was planimetered during early diastole using a commercially available image analyser (Echo-comp, Digisonics Inc., Houston, USA). The location of the calcium deposits was identified and their amount was graded by previously described morphological criteria; that is, the extent was determined by the percentage of the valvular circumference containing the deposits (grade 0 = no calcification, grade 1 = < 25%, grade 2 = 25 to 50%, grade 3 = 51 to 75%, grade 4 = >75%).[8]

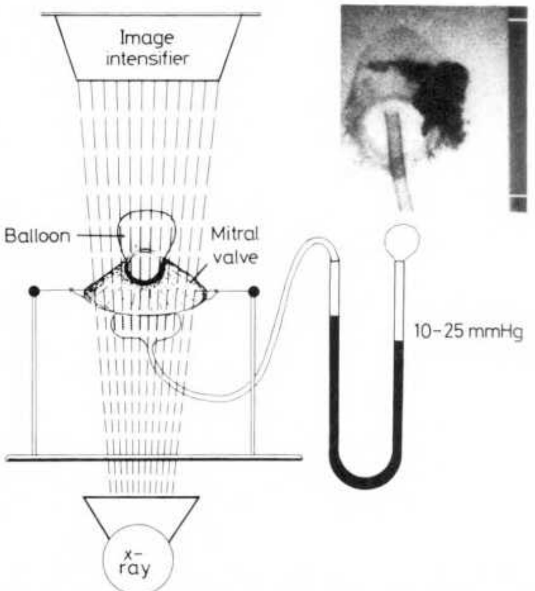

Fig. 1 *Proposed method for morphometric analysis (schematic drawing). The stenotic mitral valve removed intact during operation is placed on a specially constructed mounting. The orifice is stabilised with an airfilled balloon of known pressure. Then a radiograph is taken, directing the* x*-ray beam perpendicular to the mitral valve orifice. Upper right part: excised mitral valve including a scale after* x*-ray exposure. The mitral valve orifice as well as the calcifications are clearly visualised.*

Statistical analysis of the mitral valve area was performed with the paired Student's t test. The correct correspondence in orifice shape and in the localisation of calcification was judged at the end of the study by the two independent investigators.

Results

The results of the correlative two dimensional echocardiographic and postoperative evaluation are summarised in the Table. Five of 51 patients were excluded from the study because of technically inadequate echocardiographic recording. In six further patients no pathological specimen was available because either open commissurotomy was performed or the valve had to be cut into pieces at the time of excision.

VALVE ORIFICE AREA

Fig. 2 shows the relation between the mitral valve

Table *Data obtained from 40 patients with mitral stenosis using two dimensional echocardiography and direct measurement of valve*

Case No.	*Sex*	*Age (y)*	*Mitral valve area*			*Localisation of calcium-2DE*	*Localisation of calcium-po*	*%/degree of calcification-2DE*	*%/degree of calcification-po*
			Area-2DE (cm²)	*Area-po (cm²)*	*Area-io (cm²)*				
1	F	65	1·3	1·4	—	AL, PL	AL, PL	80% grade 4	80% grade 4
2	F	60	1·45	1·4	1·35	AL, MC	AL	60% grade 3	70% grade 3
3	M	59	3·7	3·0	—	PL	PL	10% grade 1	5% grade 1
4	M	52	1·6	1·8	—	AL, MC	AL, MC	20% grade 1	25% grade 1
5	M	57	1·8	1·7	2·3	PL, LC	AL, LC	25% grade 1	25% grade 1
6	F	58	1·6	1·3	—	AL, PL, MC, LC	AL, PL, MC, LC	90% grade 4	90% grade 4
7	F	61	2·35	2·1	—	AL, LC	AL, LC	60% grade 3	60% grade 3
8	M	55	1·7	1·8	2·3	AL, LC	AL	80% grade 4	60% grade 3
9	F	55	1·45	1·4	1·15	PL, MC	PL, MC	25% grade 1	35% grade 2
10	M	56	2·05	1·85	2·25	AL, PL	PL, LC, MC	60% grade 3	60% grade 3
11	M	57	1·6	1·6	1·35	AL, MC	AL, MC	40% grade 2	50% grade 2
12	F	59	1·55	1·85	2·25	AL, LC	AL, LC	40% grade 2	20% grade 1
13	M	60	2·25	3·1	—	PL, MC	PL, MC	30% grade 2	40% grade 2
14	F	60	1·75	1·55	1·75	PL	LC	30% grade 2	25% grade 1
15	F	58	1·3	1·4	—	PL	AL, PL	30% grade 2	50% grade 2
16	F	59	2·6	2·65	—	AL, PL, MC, LC	AL, PL, MC, LC	80% grade 4	80% grade 4
17	F	52	2·8	2·9	—	AL	AL	70% grade 3	70% grade 3
18	F	63	1·85	2·0	1·55	AL, MC	AL, MC	45% grade 2	45% grade 2
19	F	36	1·25	1·0	—	MC	MC	20% grade 1	20% grade 1
20	M	57	2·75	2·6	—	PL, MC, LC	MC, LC	50% grade 2	20% grade 1
21	F	45	1·2	1·25	1·15	PL	PL	10% grade 1	10% grade 1
22	F	39	2·25	2·2	2·85	AL, MC	AL, MC	30% grade 2	30% grade 2
23	M	44	1·7	1·85	2·25	PL, MC	PL, MC, LC	70% grade 3	40% grade 2
24	F	41	1·5	0·95	0·95	AL	AL	20% grade 1	20% grade 1
25	F	45	1·25	1·0	2·0	MC, LC	MC, LC	30% grade 2	30% grade 2
26	F	45	1·0	1·3	1·35	AL	—	20% grade 1	0% grade 0
27	F	54	1·5	1·35	1·35	AL	AL	55% grade 3	55% grade 3
28	F	49	1·5	1·35	2·25	AL, MC, LC	AL, MC, LC	25% grade 2	50% grade 2
29	F	46	1·5	1·4	—	AL	AL	40% grade 2	20% grade 1
30	F	49	1·35	1·4	2·0	AL, MC	AL	55% grade 3	20% grade 1
31	F	58	2·8	2·9	—	AL, PL	AL, PL	80% grade 4	60% grade 3
32	F	53	2·2	2·25	—	AL, LC	AL, LC	60% grade 3	50% grade 2
33	F	52	0·8	0·75	—	AL, PL, MC, LC	AL, PL, MC, LC	100% grade 4	100% grade 4
34	F	57	2·45	2·8	—	PL	PL	40% grade 2	40% grade 2
35	M	44	1·5	1·4	—	AL, PL, LC	AL, PL, LC	70% grade 3	70% grade 3
36	F	50	1·5	1·4	—	AL, PL, MC, LC	AL, PL, MC, LC	80% grade 4	80% grade 4
37	F	41	1·45	1·4	—	LC	LC	60% grade 3	60% grade 3
38	F	69	0·6	0·6	—	AL	AL	50% grade 2	50% grade 2
39	F	56	1·4	1·4	—	LC	LC	60% grade 3	60% grade 3
40	M	52	1·55	1·25	1·55	AL, LC	AL, LC	70% grade 3	70% grade 3

Abbreviations: Area-2DE, -po, -io, mitral valve area, obtained with two dimensional echocardiography, postoperatively, intraoperatively; AL, PL, anterior, posterior leaflet; MC, LC, medial, lateral commissure.

orifice area measured by two dimensional echocardiography and the mitral valve area measured postoperatively in 40 patients. The valve areas derived from two dimensional short axis views were between 0·62 and 3·7 cm², the mean value being 1·74±0·61 cm². The correlation coefficient between these values and the areas obtained postoperatively was extremely good (r=0·92). The standard error of estimate was below 0·3 cm² and the maximum difference between the echo and postmortem estimates in any pair of estimates was 0·85 cm².

In 19 of 40 patients intraoperative estimates of size of the mitral valve using Hegar dilators with known diameters was also performed. The relation between these measurements and the planimetered orifice areas of the excised mitral valves is depicted in Fig. 3. The correlation coefficient was 0·63 and the standard error of estimate (SEE) was 0·42 cm². The relation between the areas determined by two dimensional echocardiography and the values obtained during operation was in the same range, the correlation coefficient being 0·58 (SEE=0·44 cm²).

VALVE ORIFICE SHAPE: LOCALISATION OF CALCIFICATION

The shape of the stenosed mitral orifice, which was analysed in 40 patients, was not uniform but often showed bizarre configurations. Representative examples obtained by both methods are shown in Fig. 4.

A precise agreement in orifice shape between preoperative two dimensional echocardiograms and x-rays of the excised mitral valve was found in 34

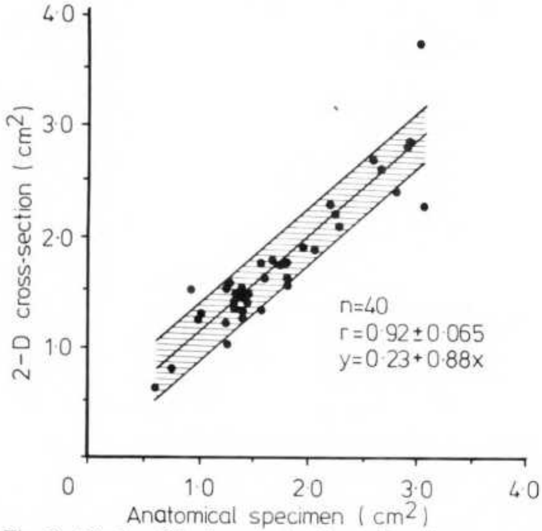

Fig. 2 *Display of the data obtained from 40 patients correlating the mitral valve areas calculated with two dimensional echocardiography with* x-ray *exposure of the anatomical specimen. (SEE is within the shaded area.)*

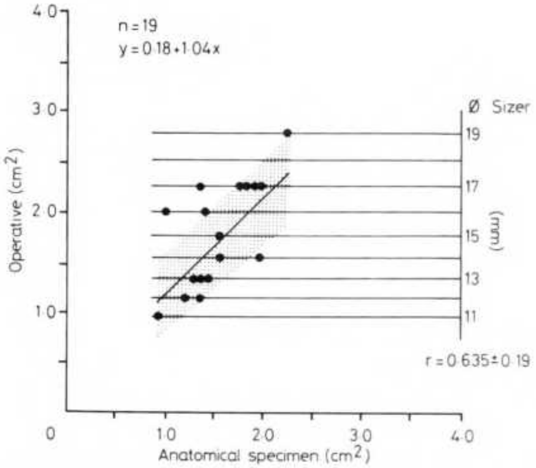

Fig. 3 *Relation between the areas obtained during operation using a sizer of known diameter and the* x-ray *picture of the excised mitral valve. (SEE is within the shaded area.)*

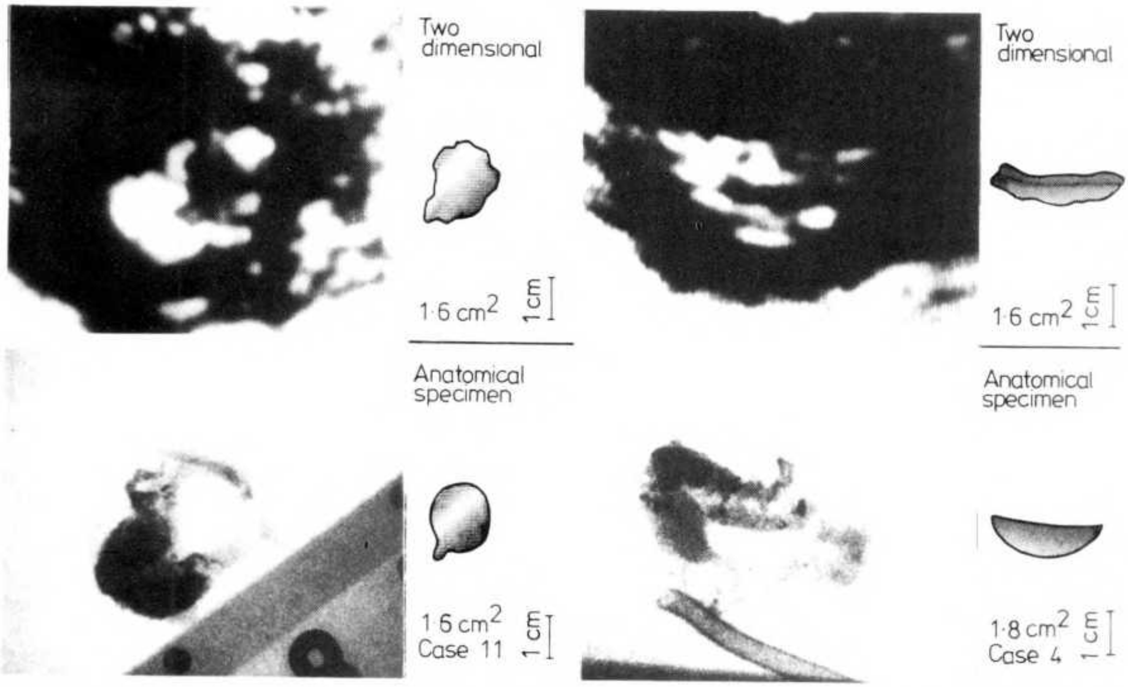

Fig. 4 *Examples of preoperative short axis views of the stenotic mitral valve (above) and of corresponding* x-rays *of the valve after replacement (below), showing good agreement in shape and calcium localisation.* — *=1 cm.*

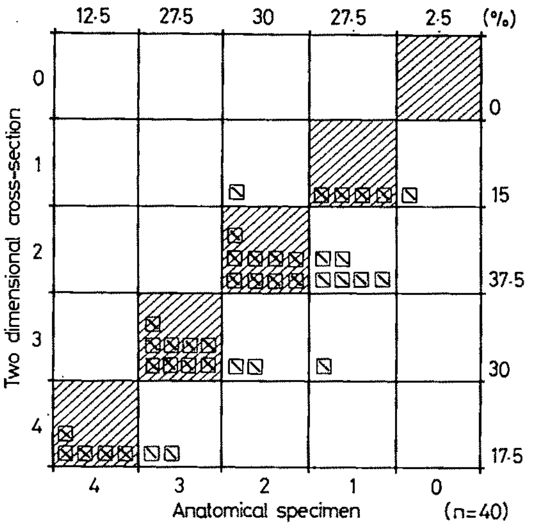

Fig. 5 *Graph showing the correlation of the degree of valve calcification determined with two dimensional echocardiography with* x-*ray exposure of the anatomical specimen. A grading system 0–4 was used (see text). The shaded areas indicate agreement with both methods. The amount of calcific deposits was partly overestimated by two dimensional echocardiography (clear fields to the right).*

patients (85%). In the remaining six patients the two independent investigators judged the echocardiographic findings as incorrect.

Areas of calcification were echocardiographically identified as dense conglomerate echoes and were broadly evident in all 40 patients. Calcification could be morphologically confirmed in 39 of 40 patients. The echocardiogram showed the exact localisation of these calcium deposits on the anterior and posterior mitral leaflet, and on the medial and lateral commissure in 30 patients (75%) (Table).

DEGREE OF CALCIFICATION

Thirty-nine excised mitral valves showed some degree of calcification (Table). With application of the proposed system (grade 0 to 4) agreement with both methods was found in 27 of 40 patients (67%). With this classification the degree of calcification was overestimated with two dimensional echocardiography in 12 patients (Fig. 5). But this overestimation was not statistically significant. In only 10 patients (25%) was the difference in severity of calcification using the two methods more than 10% (Table).

Discussion

By providing correct spatial orientation cross-sectional echocardiography allows an appropriate characterisation of the mitral valve. Several studies suggest that a reliable non-invasive estimation of the severity of valve stenosis is now possible. Taking valve orifice area from the two dimensional echocardiogram, a good correlation was shown between both intraoperative estimations of size of the orifice and the mitral valve area calculated by the Gorlin formula.[3–6 9]

Using a different approach, we came to similar conclusions with respect to mitral valve orifice area. Our proposed method of preparing and imaging the stenotic valve postoperatively provided the means of relating the two dimensional echocardiographic findings to the morphology of the valve. A true radiographic visualisation of the mitral valve orifice itself was possible, as with two dimensional cross-section. This method was, therefore, independent of catheterisation data and of the presence or absence of additional mitral regurgitation.

The correlation in our study was good, the correlation coefficient being 0·92 with 40 patients. These results confirm preliminary studies of Wann *et al.*[5] who measured the valve area in some pathological specimens and also found good accuracy of two dimensional echocardiography. To prevent shrinkage of the orifice, in this study the pathological specimen was fixed to its main diastolic position immediately after operation.

The discrepancies between area measurements with both methods (range 0 to 0·85 cm^2 in our study) are caused by technical limitations of the ultrasound method. One limiting factor, the varying orifice size resulting from different gain settings, has been systematically investigated and was carefully taken into account in this study.[10] Another critical point is the proper location of the transducer directly over the mitral valve orifice to avoid sloping sections of the orifice and therefore overestimation.[10 11] This factor is probably responsible for some differences between single values of the area obtained with two dimensional echocardiography in relation to the pathology of the valve.

Another limitation of the method was that during x-ray exposure of the excised mitral valve an airfilled balloon was inserted to avoid shrinkage of the orifice, which may lead to an overextension of the orifice. The data, however, do not confirm this difficulty because with two dimensional echocardiography there is overestimation rather than underestimation of the valve area. It is unlikely that a rigid stenotic mitral valve orifice reacts much to low pressure balloon extension.

The good correlation between the mitral valve area shown on cross-sectional scanning and the orifice area derived from pathological specimens contrasts, to some extent, with the intraoperative measurements. Whereas Henry *et al.*[3] found an excellent correlation between echocardiography and intraoperative estimation of size, our correlation coefficient was only 0·53.

One explanation for these discrepancies is that in our study no custom-built estimator of size was used for the area measurements. The orifice area was instead derived from the largest diameter of the orifice obtained during the operation. One further possible reason is that in our investigation the valve circumference mostly showed a bizarre configuration, unsuitable even for a specially preformed estimator of size.

Other investigators also emphasise the methodological difficulties inherent in the intraoperative estimation of size of stenosed mitral valves.[4 5] Wann *et al.*[5] for example had been unable to develop a satisfactory method for measuring the mitral valve area during operation for comparison with two dimensional echocardiography.

The structural architecture of the mitral valve and the presence or absence of calcification, as well as pliability of the leaflets, are important factors in determining whether a patient with mitral stenosis is a candidate for commissurotomy.[12 13] Our findings indicate that a detailed morphological analysis of the mitral valve orifice is echocardiographically possible. An exact correspondence in shape was found in 85% of patients when correlating the data to the postoperative radiographic findings. Moreover, in 75% the exact localisation of the calcium deposits was possible. In this regard two dimensional echocardiography in long and short axis planes seems to be superior to preoperative *x*-ray examination. With the latter method, leaflet calcification may be readily confused with annular calcium, which need not necessarily affect the mobility of the cusps.[13]

In rheumatic mitral valve disease the thickening and calcification of the valve tend to spread from the tips towards the base of the leaflets.[14] The tomographic short axis cross-sections through the mitral valve orifice are therefore suitable for detecting early calcification. Abnormally intense and globular echoes of the leaflets and commissures were identified as calcium deposits. A similar echo pattern was described by Schwartz *et al.*[15] doing in vitro studies with M-mode echocardiography in calcified and noncalcified valves.

With application of the grading system proposed by Lachman and Roberts[8] the amount of calcium could be reliably determined by two dimensional echocardiography. These results confirm earlier studies, performed with the M-mode technique, which also semiquantified the calcification of mitral leaflets.[16-18] But the exact quantification and localisation of echoes is sometimes difficult with the M-mode method. Multiple echoes generated by heavily calcified valves make it impossible to distinguish reliably echoes produced by the posterior cusp from those produced by the anterior leaflet.

Though not statistically significant some overestimation of the amount of calcium was obtained with two dimensional echocardiography. These false positive results can be accounted for by extensive fibrosis and thickening of cusps which produce a similar echo pattern. According to first reports by Rogers *et al.*[19] the estimation and differentiation of tissue calcium can be further enhanced by digital processing of ultrasound signals. The application of this method to patients with atherosclerotic coronary arteries leads to an improvement of tissue characterisation in comparison with conventional techniques.

In conclusion, two dimensional echocardiography allows detailed morphological studies of stenotic mitral valves. The degree of mitral stenosis can be reliably determined by means of planimetry. Furthermore, an assessment of the shape of the valve orifice and of the degree and localisation of calcification is possible. These non-invasive data are of special importance for planning operative treatment.

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Evaluation of left ventricular performance during supine exercise by transoesophageal M-mode echocardiography in normal subjects

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SUMMARY In order to evaluate left ventricular function during dynamic exercise transoesophageal M-mode recordings of the left ventricle were carried out with a newly developed transducer gastroscope system. Twelve healthy subjects performed a graded supine bicycle exercise test. Stable and good quality images of the left ventricle at rest and during exercise at different steps up to a maximum workload of 100 watts were obtained in all patients. Isotonic maximum exercise resulted in a significant increase in fractional shortening of the left ventricle, peak shortening rate, and peak lengthening rate of the left ventricular minor axis. Left ventricular end-diastolic dimension decreased significantly. With increasing workload the pressure rate product increased significantly. It is concluded that transoesophageal M-mode echocardiography is a useful method of evaluating left ventricular performance during dynamic exercise.

M-mode echocardiography is an accurate and reproducible technique for assessing left ventricular size and performance at rest in normal sized hearts without segmental wall motion abnormalities.[1–4] The technique, however, is severely limited by the difficulty of obtaining high quality echocardiograms of the left ventricle during dynamic exercise.[5–7] In order to overcome this restriction transoesophageal left ventricular echocardiograms at rest and during dynamic exercise were recorded with a newly developed transducer gastroscope system.

Subjects and methods

Twelve healthy volunteer students (seven men, five women), aged 18 to 23 years, were studied. All had a normal cardiovascular history, physical examination, and 12 lead electrocardiogram at rest and during maximum exercise. None of the subjects was taking any drugs. Informed consent was obtained from them all.

TRANSDUCER GASTROSCOPE SYSTEM

A 3·5 MHz non-focused Aerotech ultrasound transducer fixed to the tip of a commercially available gastroscope with an outer diameter of 7 or 9 mm (Fig. 1) was used. The transducer was mounted in a 24×14×11 mm³ casing with rounded edges for easy swallowing. The tip of the gastroscope could be angulated in all directions and fixed in a definite position by means of two knobs at the proximal end of the gastroscope (Fig. 1). Thus, a close contact between the transducer and the moist surface of the mucosa of the oesophageal wall was guaranteed without the need for a coupling agent.

TRANSOESOPHAGEAL EXAMINATION TECHNIQUE

Because the fibreoptics system of the gastroscope was replaced by the transducer cable, the gastroscope had to be introduced blind. Therefore, before the ultrasound examination, each patient had to have an x-ray examination of the oesophagus in order to exclude a diverticulum of the oesophagus. Subjects were fasted and, one hour before the examination, received 0·5 mg atropine sulphate subcutaneously to avoid reflex bradycardia and gagging. The investigation was carried out with the patient in a supine position.

After insertion of the gastroscope to a level of about

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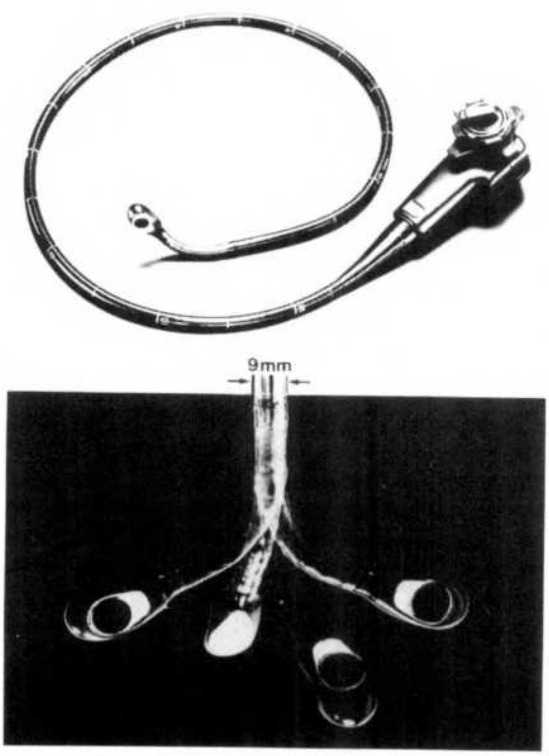

Fig. 1 *The transoesophageal ultrasound gastroscope system. The outer diameter of its shaft is 9 mm. The transducer, covered with soft plastic material, is incorporated into the tip of the gastroscope. Angulation of the transducer is possible by turning two external knobs.*

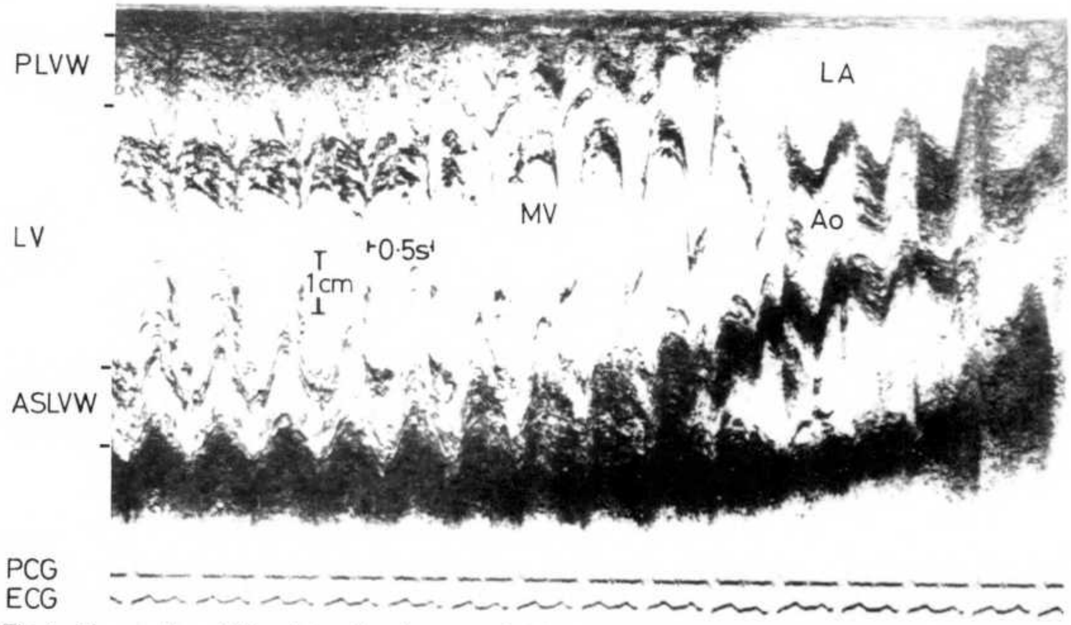

Fig. 2 *Transoesophageal M-mode scan from the aorta to the left ventricle at the level of the papillary muscle. Ao, aorta; ASLVW, anteroseptal wall of the left ventricle; ECG, electrocardiogram; LA, left atrium; LV, left ventricle; MV, mitral valve leaflets; PCG, phonocardiogram; PLVW, posterior wall of the left ventricle.*

40 cm, the aortic root echo could be identified. Advancing 1 to 2 cm further and rotating counter clockwise permitted recordings of the left ventricle at rest and during exercise at the level of the free edges of the mitral leaflets (Fig. 2), thus showing the posterior and the free anteroseptal walls.

Each subject performed a supine bicycle exercise test at workloads of 25, 50, 75, and 100 watts. The load was increased stepwise at three minute intervals. Left ventricular echocardiograms and blood pressures were simultaneously recorded at rest and at the third minute of each workload level.

The transoesophageal echocardiographic examination took about 20 minutes for each patient. There were no complications.

ECHOCARDIOGRAPHIC MEASUREMENTS AND CALCULATIONS

Transoesophageal echoes were recorded on standard echocardiographic equipment at a paper speed of 50 or 100 mm/s. The recorded echocardiograms were digitised and processed, using a previously described computerised method.[8]

Echocardiographic variables of particular interest in this study were:

(a) End-diastolic left ventricular diameter (DD in mm), measured at the onset of the R wave.

(b) End-systolic diameter (DS in mm). The smallest distance between the posterior and the anteroseptal wall of the left ventricle.

(c) Fractional shortening (FS as %) of the minor axis of the left ventricle, calculated according to the following formula:

$$\mathrm{FS}=\frac{\mathrm{DD}-\mathrm{DS}}{\mathrm{DD}}\times 100$$

(d) Peak shortening rate ($\mathrm{VCF_{max}s^{-1}}$) of the left ventricular minor axis:

$$\mathrm{VCF_{max}}=\left(\frac{1}{\mathrm{D}}\times\frac{\mathrm{dD}}{\mathrm{dt}}\right)_{\mathrm{min}}$$

(e) Peak lengthening rate ($\mathrm{VLR_{max}s^{-1}}$) of the left ventricular minor axis:

$$\mathrm{VLR_{max}}=\left(\frac{1}{\mathrm{D}}\times\frac{\mathrm{dD}}{\mathrm{dt}}\right)_{\mathrm{max}}$$

In each subject, three successive cardiac cycles at rest and at different levels of exercise were analysed and averaged. Statistical analysis was carried out using Friedmans's test for examination of the general tendency of the data and Wilcoxon's test to analyse the step-to-step difference between the control measurements and those at the different workloads.

In accordance with recent data by Matsumoto *et al.*[9] we found a good correlation between the left ventricular diastolic dimensions measured by the transoesophageal approach and the standard transthoracic method (r=0·90; standard error of estimate ±4·1 mm). In order to assess the reproducibility of the transoesophageal measurements the gastroscope was drawn back up to the level of the ascending aorta and introduced a second time in order to identify the largest left ventricular minor axis in eight subjects (Fig. 3, r=0·90; standard error of estimate ±2·25 mm).

Results

The mean values of the echocardiographic variables at rest and at the different levels of workload are listed in the Table for all 12 subjects. Fig. 4 represents typical recordings of a normal subject at rest and during exercise. Results for relevant echocardiographic variables are shown in Fig. 5.

Dynamic exercise resulted in a significant increase in heart rate (89±13 up to 142±22/min; $p<0{\cdot}01$), systolic blood pressure (132±9 up to 155±13 mmHg; $p<0{\cdot}01$) and, accordingly, in the pressure rate product (11 800±2100 up to 22 100±4840 mmHg/min; $p<0{\cdot}01$) from rest to the endpoint of exercise. Left ventricular end-diastolic dimension decreased significantly from 52±6 mm at rest to 48±7 mm after three minutes of 100 watts ($p<0{\cdot}01$). The decline in systolic dimension was even more pronounced, resulting in a steady increase in fractional shortening (36±4

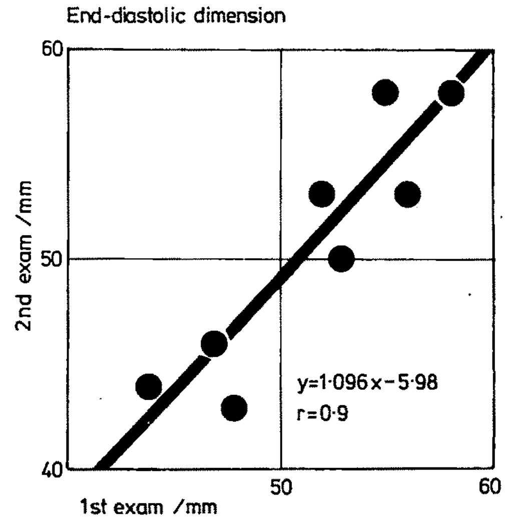

Fig. 3 *Comparison between transoesophageal echocardiographic left ventricular end-diastolic dimension of two independent examinations in the same subject (n=8).*

Table *Mean values (±1 standard deviation) of different echocardiographic variables in 12 normal subjects (Friedman's test performed for the analysis of central tendency of sequential data)*

	Rest	*3' 25W*	*3' 50W*	*3' 75W*	*3' 100W*	*Friedman test*
Heart rate/min	89±13	106±13	117±15	131±19	142±22	p<0·001
Systolic blood pressure (mmHg)	132±9	135±9	140±14	149±15	155±13	p<0·001
Pressure rate product (mmHg/min×10^3)	11·8±2·1	14·4±2·0	16·3±2·8	19·6±4·5	22·1±4·8	p<0·001
End-diastolic diameter (mm)	52±6	51±7	49±6	48±7	48±7	p<0·01
End-systolic diameter (mm)	33±6	32±6	30±6	28±6	27±6	p<0·001
Fractional shortening (%)	36±4	38±4	40±5	42±5	44±5	p<0·001
$VCF_{max}s^{-1}$	2·4±0·3	2·7±0·4	3·0±0·5	3·6±0·9	4·2±1·0	p<0·001
$VLR_{max}s^{-1}$	4·0±0·9	4·6±0·9	5·2±0·9	6·1±1·2	7·0±1·7	p<0·001

VCF_{max}, peak shortening rate of the left ventricle; VLR_{max}, peak lengthening rate of the left ventricle.

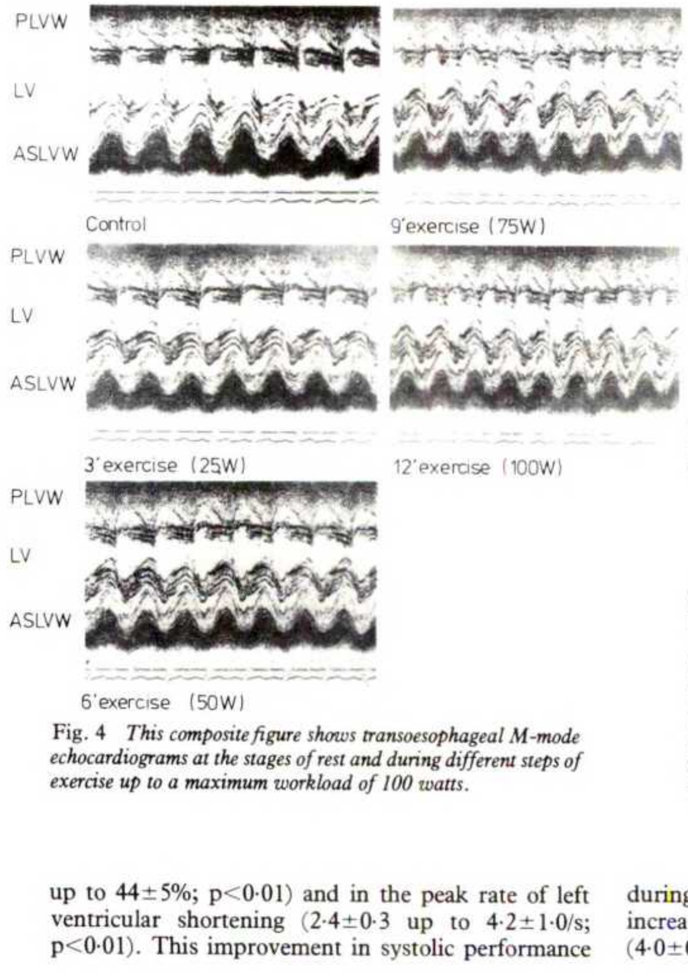

Fig. 4 *This composite figure shows transoesophageal M-mode echocardiograms at the stages of rest and during different steps of exercise up to a maximum workload of 100 watts.*

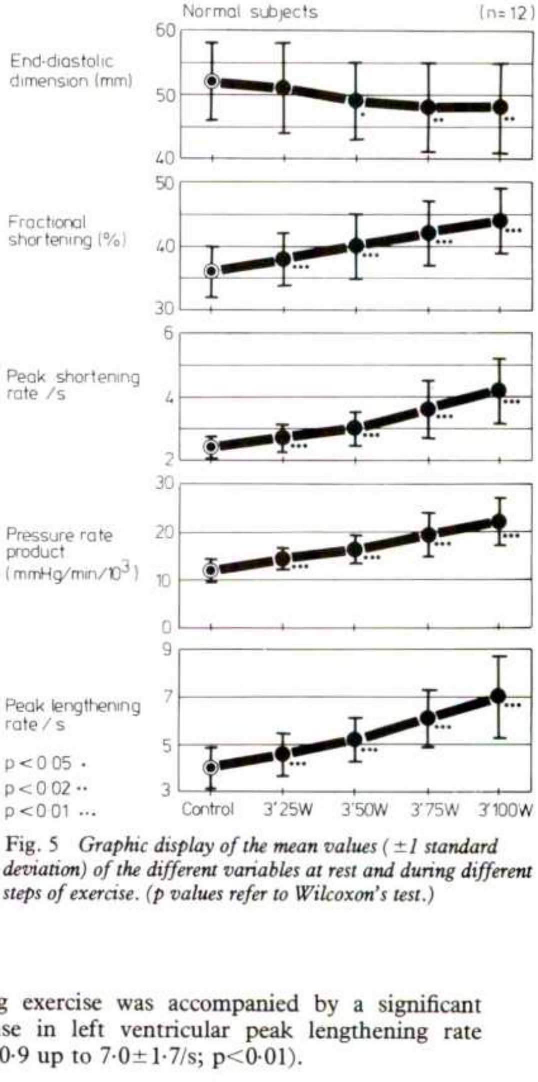

Fig. 5 *Graphic display of the mean values (±1 standard deviation) of the different variables at rest and during different steps of exercise. (p values refer to Wilcoxon's test.)*

up to 44±5%; $p<0·01$) and in the peak rate of left ventricular shortening (2·4±0·3 up to 4·2±1·0/s; $p<0·01$). This improvement in systolic performance during exercise was accompanied by a significant increase in left ventricular peak lengthening rate (4·0±0·9 up to 7·0±1·7/s; $p<0·01$).

Discussion

The main purpose of this study was to document the usefulness and the advantages of exercise transoesophageal echocardiography. Since the first clinical application of transoesophageal echocardiography by Frazin *et al.* in 1976,[10] a few studies only have appeared on the evaluation of left ventricular function at rest by the transoesophageal approach. This was partly because of the unusual character of the technique and partly because of problems of transducer control.[9 11-17] In order to apply the technique further to exercise evaluation of left ventricular function, the transducer system had to be improved. The incorporation of the ultrasound transducer into the tip of a gastroscope enabled controlled manipulation of transducer orientation (rotation and angulation) which made the recording of left ventricular exercise echocardiograms much easier. Published reports of exercise echocardiography using the parasternal approach[5 6 18-22] indicate technical problems in obtaining adequate images. These difficulties are usually caused by chest wall movement and by the interposition of lung tissue between the transducer and the heart resulting from exercise-induced hyperventilation. The major advantages of the method described in this paper are that, because of the close anatomical relation of the oesophagus and heart, respiration and chest wall movement do not interfere with left ventricular imaging.

Our echocardiographic investigation disclosed a progressive decrease in end-systolic dimension during dynamic exercise, corresponding to an increase in stroke volume. This is in agreement with recent angiographic and radionuclide studies.[23-25] The concept that an increase in stroke volume seems to be the normal response to dynamic exercise is thus supported and is thought to be caused by an increased contractility.[26-28] This is indicated in our results by a significant increase in left ventricular fractional shortening as well as in the peak shortening rate of the left ventricular minor axis. The end-diastolic diameter, on the other hand, did not increase, so that the Frank-Starling mechanism seems to have no influence on the improvement of left ventricular systolic performance during *supine* exercise in normal subjects. The reasons for the decrease in end-diastolic dimension are probably related to a decrease in filling time with increasing heart rate and to an activation of the sympathetic tone, as has already been pointed out.[23 24 26-29]

This study shows that high quality transoesophageal M-mode echocardiograms of the left ventricle at rest and during dynamic exercise can be obtained. The technique has the advantage of being non-invasive, repeatable, and inexpensive. It allows study of instantaneous events in each cardiac cycle rather than the results in several cycles needing to be combined. There is no radiation exposure involved and, because of the high resolution of the ultrasound technique, the evaluation of cavity dimension and wall thickness changes can be assessed more easily than with gated blood pool scans or the other techniques now available.

Although transoesophageal echocardiography does give rise to some discomfort for the patient, and skill is required to introduce the ultrasonic probe into the oesophagus, the high success rate, good stability, and the quality of continuous left ventricular images more than make up for the disadvantages.

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Br Heart J 1982; **48**: 67–72

Transoesophageal cross-sectional echocardiography with a phased array transducer system
Technique and initial clinical results

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SUMMARY Cardiac imaging by transthoracic two dimensional echocardiography is impaired in patients with chronic lung disease, those with obesity, and those with abnormal chest wall configuration. In order to overcome these limitations, a miniature phased array ultrasound transducer fitted to the tip of a commercially available gastroscope was developed. Transducer position and orientation can be adjusted completely by external control of vertical displacement inside the oesophagus, rotation, and angulation. Introduction and operation of the transducer gastroscope system are usually well tolerated by the patients, since no mechanical vibrations are generated and there is no need for an oil bag to secure oesophageal wall contact. Cardiac images of high quality are obtained even from structures and regions that are poorly or not at all imaged from external transducer positions.

Two dimensional echocardiography with its wide field of view and high degree of spatial orientation is by now a well established technique in the morphological and functional evaluation of various cardiac disorders. It has frequently been reported, however,[1-3] that the main limitation of two dimensional echocardiography is the poor image quality obtained in patients with a difficult chest configuration, particularly in those with obesity, emphysema, and chronic obstructive pulmonary disease. Even in normal patients it is sometimes difficult to obtain two dimensional images of diagnostic quality from certain cardiac structures (for example the interatrial septum or the cardiac apex).

The recent development of a miniature ultrasonic phased array probe for transoesophageal imaging of the heart[4] offers a promising means to circumvent the problems of conventional transthoracic two dimensional echocardiography.

Subjects and methods

TRANSOESOPHAGEAL TRANSDUCER ARRAY

The transducer array for transoesophageal applications consists of 32 linearly arranged elements with a centre frequency of 3·5 MHz, corresponding to a wavelength of 0·43 mm. The total aperture of the array is approximately 9 mm, and a 90° sector for real time imaging is obtained by appropriate phasing of the single elements.[5 6] For the contacting surface of the transducer system a spherical acoustic lens was chosen, which gives a depth of field from 2 to 10 cm in front of the array.

The transducer system is embedded in soft plastic material with carefully rounded edges to avoid damage to the oesophagus, and it is fitted to the distal end of a commercially available gastroscope (Fig. 1). The only rigid part of this new ultrasonic endoscope is represented by the outer dimensions of the transducer array: 35 mm long, 15 mm wide, and 16 mm thick.

Rotation of the gastroscope and transducer angulation is feasible by external control, thus yielding a high degree of freedom for transducer manipulation. In order to operate the transoesophageal phased array scanner, it was connected to a Varian 3400 or 3400R ultrasonic system. All studies were recorded in real time on one-inch videotape.

EXAMINATION TECHNIQUE

The system was evaluated in 26 patients (12 women, 14 men), ranging in age from 22 to 72 years. In order

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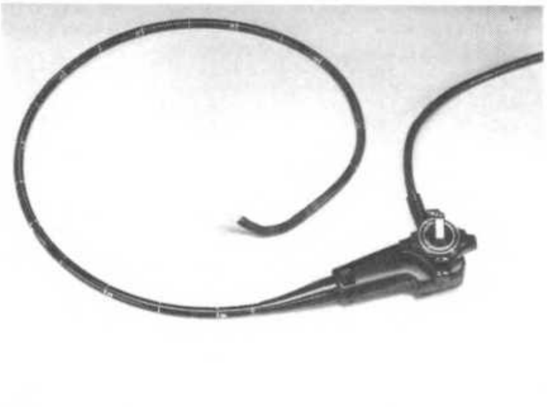
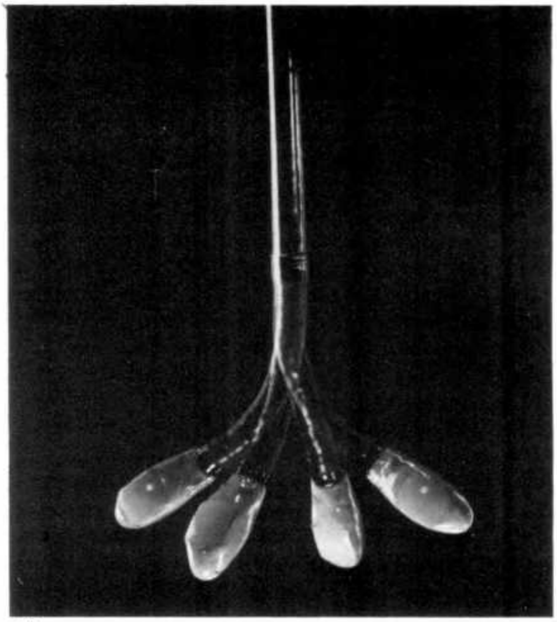


(a)

Fig. 1 *(a) The ultrasonic endoscope. A miniature phased array transducer is fixed at the flexible tip of a commercially available gastroscope. Transducer orientation can be adjusted by the external control unit at the proximal end of the gastroscope. (b) Photomontage showing transducer angulation in two orthogonal planes.*



(b)

to rule out a diverticulum of the oesophagus, all patients had a barium swallow beforehand. Written informed consent was obtained from each patient.

Patients were fasted for about eight hours and were given 0·5 mg atropine sulphate one hour before the investigation in order to avoid bradycardia and hypersalivation. Immediately before the gastroscope was inserted the patients were given 10 mg diazepam intravenously. The transoesophageal study was then performed with the patient supine. Apart from slight gagging no complications were encountered, as the patients usually swallowed the ultrasonic gastroscope as easily as they would a normal endoscopic fibrescope. Cardiac images of high quality were observed when the transducer array was inserted to a level of about 40 cm.

Results

The first cardiac structure that is readily identified with the gastroscope is the aortic root which is shown in the diastolic frame of Fig. 2. All three cusps are visible, and part of the left ventricular outflow tract as well as the right ventricular outflow tract are clearly outlined. A slight counterclockwise rotation of the gastroscope shows the mitral valve with both leaflets, left atrium and ventricle, and the interventricular septum (Fig. 3). Further descent of the gastroscope allows the left ventricle to be seen in several cross-sectional views at different levels of the left ventricu-

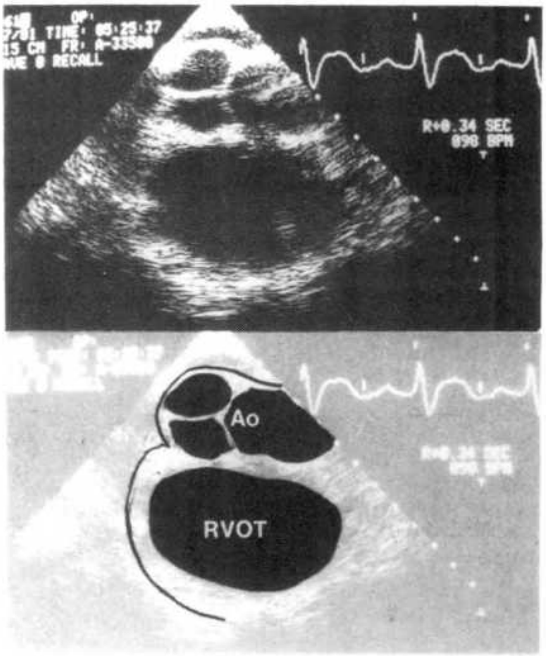


Fig. 2 *Stopframe image of transoesophageal cross-sectional echocardiogram at the level of the aortic root during isovolumic contraction. The three cusps are clearly visible, as well as the right ventricular outflow tract (RVOT) and part of the left ventricular outflow tract.*

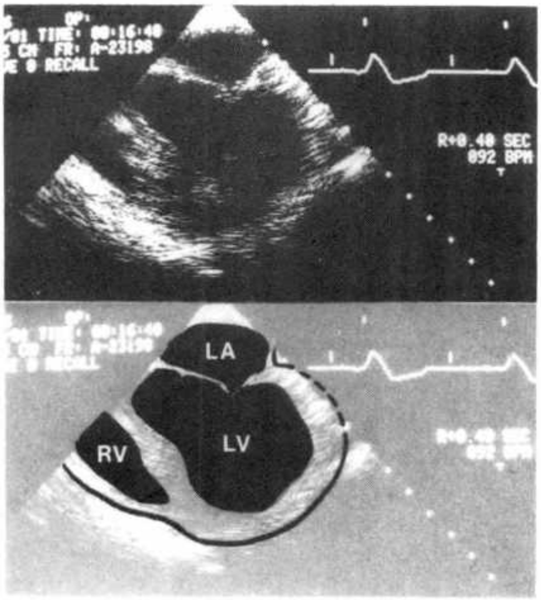


Fig. 3 *Systolic stopframe image of transoesophageal cross-sectional echocardiogram at the level of the mitral leaflets. Note the proximity of the left atrium (LA) to the ultrasonic transducer at the sector apex, while the left ventricle (LV) and part of the right ventricle (RV) are imaged below the left atrium.*

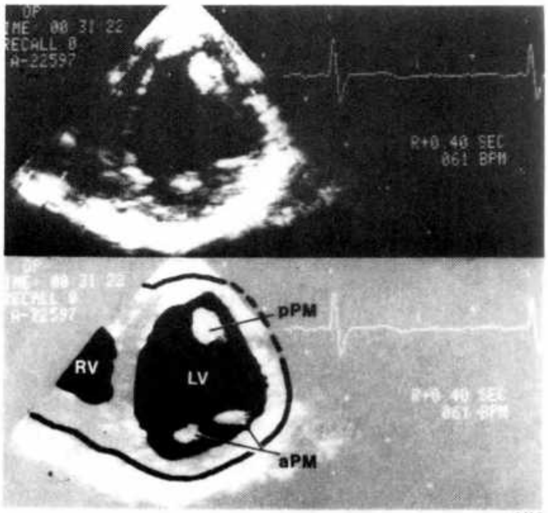


Fig. 4 *Transoesophageal short axis cross-sectional view of the left ventricle at the level of the papillary muscles. aPM, anterior papillary muscle; pPM, posterior papillary muscle.*

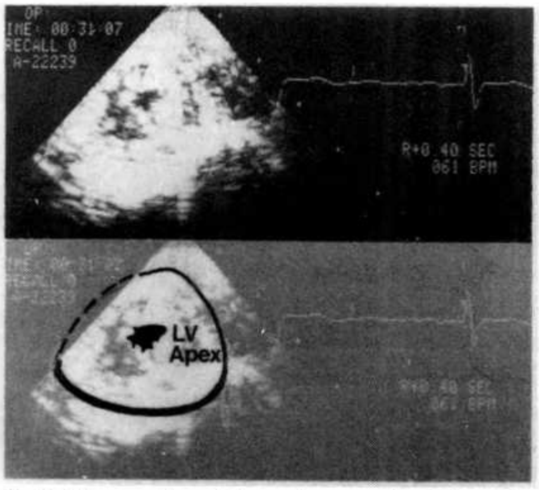


Fig. 5 *Transoesophageal short axis cross-sectional view of the left ventricle at the level of the cardiac apex.*

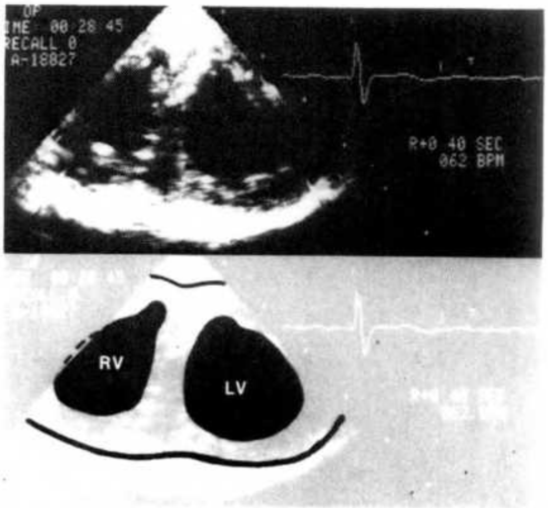


Fig. 6 *Transoesophageal cross-sectional view of both ventricles within the 90° sector scan.*

lar long axis, for example at the level of the papillary muscles (Fig. 4) or at the cardiac apex (Fig. 5). With a non-dilated left ventricle both ventricles can usually be viewed within the 90° sector (Fig. 6), thus making it possible to differentiate the right side of the heart by peripheral venous injection of an ultrasonic contrast agent such as agitated saline (Fig. 7).

By clockwise rotation of the gastroscope at the atrioventricular junction the left and right atrium and the tricuspid valve are identified (Fig. 8). In contrast

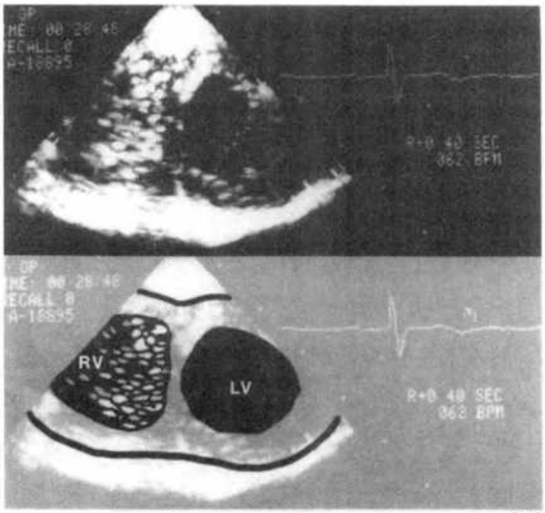


Fig. 7 *Same echocardiographic view and same patient as shown in Fig. 6. Because of a peripheral venous injection of agitated saline dense echo contrast appears in the right ventricle.*

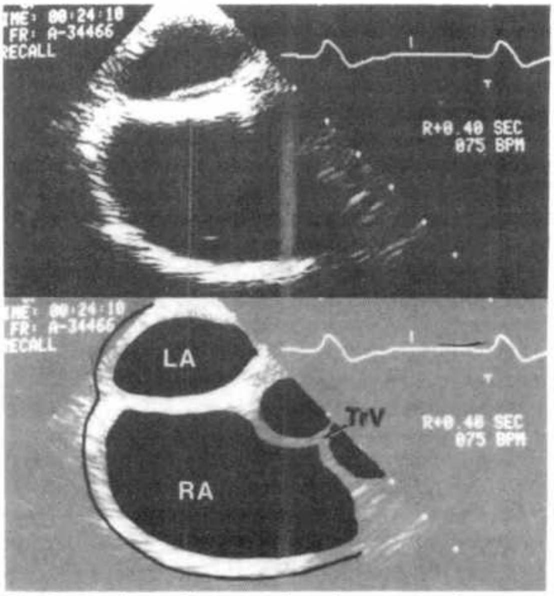


Fig. 8 *Stopframe of transoesophageal cross-sectional echocardiogram at the level of the atrioventricular junction. Both atria and the interatrial septum are clearly outlined. The cross-sectional plane dissects the left atrium (LA) cranially making its area appear smaller than that of the right atrium (RA). TrV, tricuspid valve.*

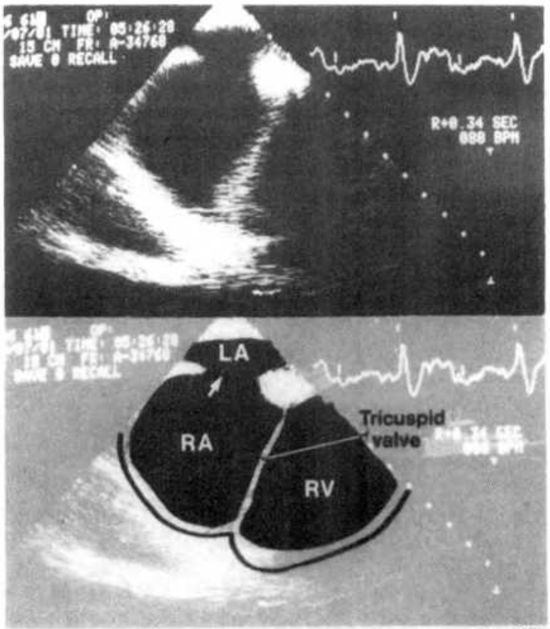


Fig. 9 *Transoesophageal cross-sectional view of the right side of the heart in a patient with an ostium secundum type atrial septal defect. The arrow in the lower panel shows the location and the diameter of the defect.*

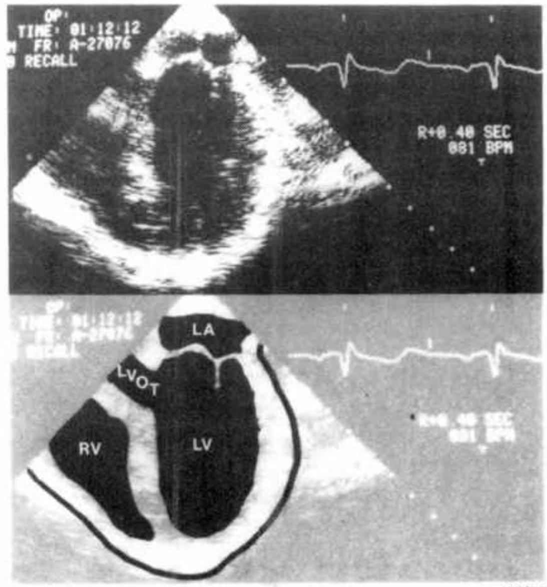


Fig. 10 *Two-dimensional transoesophageal echocardiographic image from a patient with mitral valve prolapse. The cross-sectional plane is shown at the level of the atrioventricular junction. Note the pronounced late systolic bulging of the anterior mitral leaflet into the left atrium, as compared with the normal closing position of the mitral leaflets in Fig. 3.*

to the transthoracic approach, the interatrial septum is imaged in total without echo drop-outs. This is because the ultrasonic beams hit the interatrial septum nearly perpendicularly from an oesophageal transducer position.

Thus, atrial septal defects can be detected with high diagnostic accuracy, as is the case in the ostium secundum type lesion seen in Fig. 9, where the loss of ultrasonic reflection (arrow in lower panel) corresponds to the location of the defect. Another example of the clinical usefulness of transoesophageal cross-sectional echocardiography is the diagnosis of a mitral valve prolapse, exemplified on the systolic frame of Fig. 10. The abnormal arching of the anterior mitral leaflet into the left atrium is clearly documented.

Discussion

Transoesophageal studies with the aim of assessing cardiac function were first reported in 1971 by Side and Gosling[7] who performed Doppler velocity measurements in the thoracic aorta. Five years later, Frazin *et al.*[8] presented transoesophageal M-mode recordings with a single element transducer connected to the ultrasound machine by a cable only, which therefore severely restricted ultrasonic beam orientation. Recently, Hisanaga *et al.*[9] introduced a high speed rotating ultrasound scanner to obtain cross-sectional cardiac images without hindrance from ribs, sternum, or lung tissue. The transducer housing of this system is enclosed in an inflatable oil bag to secure contact with the oesophageal wall, and it is fixed to the tip of a gastroscope-like shaft that offers no means for controlled manipulation of beam direction. Apart from this disadvantage, the oil bag and the mechanical vibrations of the rotating transducer are liable to cause discomfort to the patient.

These limitations are not present in our system. The 90° sector is generated by electronic beam steering and there is no need for an oil bag, since oesophageal contact can easily be accomplished by transducer angulation. The attachment of a single element transducer to a normal gastroscope with complete external control of oesophageal transducer orientation has already given promising results in M-mode exercise studies[10] and pulsed Doppler investigations.[11] Replacing the single element transducer by a phased array system without a significant increase of gastroscope or transducer dimensions offers new possibilities in cross-sectional cardiac imaging, particularly in cases where transthoracic echocardiography is difficult.

A sector angle of 180° as in Hisanaga's system cannot be produced by the phased array system, yet the line density within the 90° sector is obviously higher, and all cardiac structures can be imaged by rotation of the gastroscope and proper angulation of the cross-sectional plane. Moreover, introduction and operation of the phased array endoscope cause no discomfort.

In order to obtain satisfactory results with this technique we feel that about two months of gastroscopic practice are necessary, as the success rate very much depends on the skill of the investigator. In the past 15 months, we were able to introduce the gastroscope in 84 out of 103 patients scheduled for one- or two-dimensional transoesophageal echocardiography. The failure rate of 18% is the result of extremely adverse reactions of some patients to the gastroscopic procedure. In all the other patients, once the transducer gastroscope was swallowed the two dimensional images were always clear. There were no patients with abnormally large left atria compressing the oesophagus, and so the introduction of the gastroscope never caused mechanical irritation of the left atrium.

Transoesophageal cross-sectional echocardiography with a phased array transducer system appears to be of high diagnostic potential in a wide field of clinical applications. Because of the close anatomical relation of the oesophagus and the heart, an improved morphological diagnosis of atrial thrombi, atrial septal defects, mitral valve prolapse, bicuspid aortic valve, or lesions of the tricuspid valve is expected. It will also be possible to detect contraction abnormalities in apical regions of the heart.

Intraoperative monitoring of cardiac function as well as the detection of air-containing microbubbles in the cardiac chambers during myocardial reperfusion after open heart surgery are obvious applications of this new technique, now under study in our laboratory.

Future developments comprise the implementation of two orthogonal arrays or a rotatable array for improved ultrasonic assessment of left ventricular morphology as well as the integration of a fibreoptics system into the ultrasonic endoscope. This will enable visual control of oesophageal transducer position and orientation, thus making the system suitable for abdominal applications as well. This new echocardiographic technique is non-invasive in the sense that blood vessel walls remain intact and no surgery is required, though it is admittedly less pleasant than conventional transthoracic echocardiography. In our experience with more than 80 patients who have undergone transoesophageal one- or two-dimensional echocardiography, there is no risk to the patient.

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Case reports

Br Heart J 1982; **48:** 73–4

Anomalous connection of left atrial appendage with persistent left superior vena cava

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SUMMARY An unusual connection of the left atrial appendage with a persistent left superior vena cava was demonstrated at angiography in a child with a ventricular septal defect, aortic valve stenosis, and aortic isthmus stenosis; this was later confirmed at necropsy. No previous reports of this anomaly have been found.

The left sided superior vena cava disappears at a late stage both in phylogenetic and embryonic human development and its persistence is a common finding, especially in association with other congenital cardiovascular malformations and it almost invariably drains into the coronary sinus and thence into the right atrium. Occasionally a left sided superior vena cava opens into the left atrium. In the case now reported the anomalous vein entered the coronary sinus and also communicated with the appendage of the left atrium, which was unconnected with the main left atrial cavity.

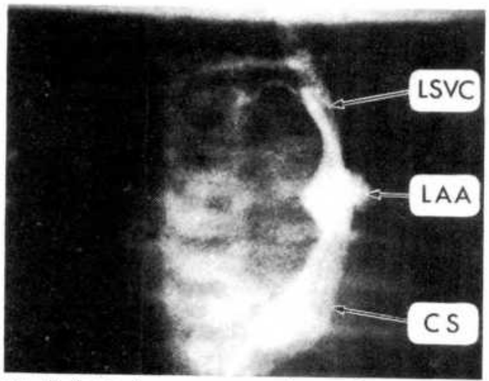

Fig. 1 *Left superior vena cava angiogram from a posteroanterior projection. LSVC, left superior vena cava; LAA, left atrial appendage; CS, coronary sinus.*

Case report

This male infant was delivered by caesarean section from a 32-year-old mother suffering from toxaemia of pregnancy, because of fetal distress as shown by tachycardia. Severe hypoglycaemia (1·2 mmol/l), was present at birth and was treated, and a cardiac murmur was noted. At the age of 1 week there was persistent tachycardia and episodes of central cyanosis were becoming increasingly frequent; the child was then referred to Killingbeck Hospital in cardiac failure.

The clinical, electrocardiographic, radiological, and echocardiographic findings suggested severe aortic valve stenosis. An angiocardiogram on admission showed a left superior vena cava draining into the coronary sinus and into the right atrium. However, and most unusually, just as it crossed the heart border, contrast escaped from it to fill part of a contracting atrium, presumably the left atrial appendage. Aortograms showed isthmus stenosis, between the left subclavian artery origin and the ductus bump, to about half of the normal diameter. The aortic valve was visualised and showed doming consistent with stenosis. At 3 weeks of age an open aortic valvotomy was performed using cardiopulmonary bypass and hypothermia; the heart, however, would not sustain the circulation on repeated attempts to come off bypass.

Necropsy showed no abnormalities apart from those of the cardiovascular system. The heart was of normal size and shape. The right atrium was of normal solitus configuration and received the normal right superior vena cava, the inferior vena cava, and a

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*LMG is supported by the National Heart Research Fund.

dilated coronary sinus, 3 mm in diameter. This coronary sinus continued into a persistent left superior vena cava which received the left jugular and subclavian veins; the innominate vein was not shown.

At the junction with the coronary sinus the left superior vena cava communicated through a 1 mm diameter opening, with a 15 mm long, 7 mm wide structure, which had the typical "glove-finger" shape and thin trabeculated wall of a solitus left atrial appendage, but there was no communication between this and the main left atrial cavity. The pulmonary veins were normal and the left atrium was normal apart from the appendicular anomaly. There was slight dysplasia of the medial portion of the tricuspid valve; the atrioventricular valves were otherwise normal.

The ventricles were of normal configuration and equal cavity size and wall thickness; they communicated through a high subcristal septal defect, 3 mm in diameter, which was immediately below the aortic valve and was partly occluded by the nodular thickened dysplastic portion of the right atrioventricular valve.

The great arteries arose in normal relation from the appropriate ventricles. The pulmonary valve was of normal size, but bicuspid. The aortic valve had been surgically split; it was thickened and nodular and no clear cusp demarcation was evident.

The ascending aorta was 4 mm in diameter, the arch was to the left, and there was pronounced preductal isthmus stenosis to 1·5 mm diameter. The aortic branches were normal.

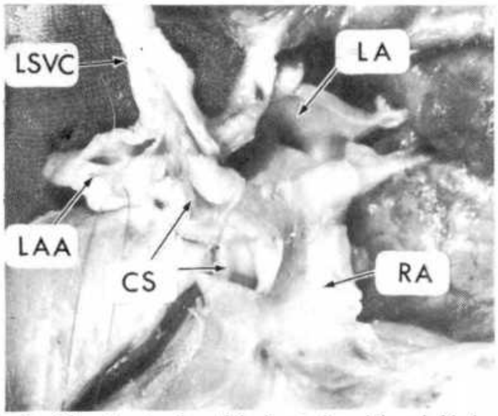

Fig. 2 *The upper portion of the heart viewed from behind. LSVC, left superior vena cava; LAA, left atrial appendage (opened); CS, coronary sinus (opened); LA, left atrium (opened); RA right atrium.*

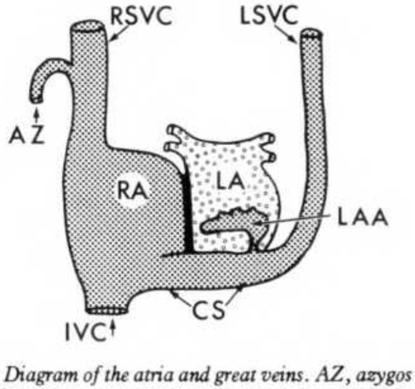

Fig. 3 *Diagram of the atria and great veins. AZ, azygos vein; IVC, inferior vena cava. Other abbreviations as in Fig. 2.*

Discussion

It is difficult to explain this anomaly in terms of embryological maldevelopment. The atrial appendages are derived from the primitive atrial chamber; the absorption of the sinus venosus into the right side of the primitive atrium brings the right atrial appendage into a position adjacent to the opening of the right superior vena cava, which is derived largely from the right lateral extension of the sinus venosus, the Cuvierian duct. The coronary sinus and, when present, the persistent left superior vena cava opening into it, are derived from the left Cuvierian duct and as the mouth of the coronary sinus opens into part of the primitive atrium it is conceivable that there could be circumstances of abnormal growth in which the left atrial appendage could be displaced to that position. In the case here described, however, the left atrial appendage joins the distal part of the coronary sinus at some distance from the right atrial opening and furthermore it has no communication with the otherwise normal left atrium. As a primary malposition appears to be unlikely it is possible that the anomaly represents a discontinuity between the left atrium and its appendage and that the communication between the appendage and the left sided vena caval–coronary sinus junction represents an expanded vein.

We are grateful to Dr O Scott, Dr J B Lynch, and Mr D R Walker for permission to publish details of this case.

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Br Heart J 1982; **48:** 75–7

Slowing of paroxysmal tachycardia with loss of functional bundle-branch block

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SUMMARY Electrophysiological studies in a patient with paroxysmal supraventricular tachycardia disclosed anterograde dual atrioventricular nodal pathways, and a concealed left-sided anomalous atrioventricular pathway which was used as the retrograde limb of two circus movement tachycardias. Tachycardia No.1, reflecting anterograde fast pathway conduction, was characterised by functional left bundle-branch block and a stable cycle length of 330 ms. Paroxysmal loss of bundle-branch block resulted in tachycardia No.2, which reflected anterograde slow pathway conduction, and was characterised by narrow QRS and a stable cycle length of 355 ms. Tachycardia No.2 had a longer cycle length than tachycardia No.1 because the increment in AH interval (slow pathway instead of fast pathway conduction) more than compensated for the decrement in ventriculoatrial interval (narrow QRS instead of bundle-branch block).

The mechanism of paroxysmal supraventricular tachycardia can usually be elucidated by detailed cardiac electrophysiological studies.[1] An important diagnostic clue is frequently provided by paroxysmal loss of functional bundle-branch block during induced supraventricular tachycardia. When the loss of bundle-branch block results in a decrement in ventriculoatrial interval, a diagnosis of atrioventricular re-entry using an anomalous atrioventricular pathway ipsilateral to the blocked bundle-branch is strongly suggested.[2] The decrement in ventriculoatrial interval is usually reflected by a decrement in the cycle length of tachycardia.[3] The decrement in cycle length, however, may be relatively small, because an increment in AH interval may partially compensate for the decrement in ventriculoatrial interval.[2]

We report a patient in whom paroxysmal loss of functional bundle-branch block during induced supraventricular tachycardia resulted in an increment in cycle length of tachycardia. The mechanism of this unusual observation is discussed.

Case report

The patient was a 33-year-old woman with mitral valve prolapse and recurrent paroxysmal supraventricular tachycardia. After informed written consent was obtained, an electrophysiological study was performed, using standard techniques and definitions.[1] Recordings during sinus rhythm (rate 67 beats/min) disclosed a short AH interval (41 ms, normal 54 to 130) and normal PA and HV intervals (36 and 52 ms, respectively). Atrial pacing from multiple sites failed to show evidence of ventricular pre-excitation.

Extrastimulus testing from the high right atrium (driven cycle length 500 ms) showed discontinuous A_1-A_2, A_2-H_2 and A_1-A_2, H_1-H_2 conduction curves, suggesting the presence of anterograde dual (fast and slow) atrioventricular nodal pathways.[4] The fast pathway was characterised by A_2-H_2 intervals of 60 to 100 ms and an effective refractory period of 380 ms, whereas the slow pathway was characterised by A_2-H_2 intervals of 165 to 260 ms and an effective refractory period of 270 ms. Extrastimuli which conducted over the slow pathway with an A_2-H_2 interval of 210 ms or longer resulted in induction of tachycardia No.2 (see below).

Incremental pacing from the high atrium at rates of 100 to 130 beats/min disclosed AH intervals of 60 to 90 ms. At an atrial paced rate of 140 beats/min, two sets of stable AH intervals (100 to 220 ms) were observed, again suggesting the presence of antero-

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Supported in part by a NHLBI Institutional Training grant, and research grants.

†Dr Rosen died after the paper was accepted.

grade dual atrioventricular nodal pathways. At atrial paced rates of 150 to 170 beats/min, AH intervals were 220 to 270 ms. Termination of atrial pacing during conduction over the slow pathway resulted in induction of tachycardia No.2 (see below).

Ventricular incremental pacing, at rates of 100 to 240 beats/min, showed intact ventriculoatrial conduction with a fixed ventriculoatrial conduction time and an eccentric sequence of retrograde atrial activation (left atrium depolarised first). These findings suggested the presence of a concealed left-sided anomalous atrioventricular pathway.[1] Termination of ventricular pacing at a rate of 240 beats/min resulted in induction of tachycardia No.1 (see below).

INDUCED SUPRAVENTRICULAR TACHYCARDIAS

Two distinct tachycardias were induced by programmed stimulation. Tachycardia No.2 (induced many times by atrial stimulation) was always characterised by narrow QRS complexes and a stable cycle length of 355 ms. During this tachycardia, the sequence of atrial activation was eccentric (distal coronary sinus, proximal coronary sinus, high right atrial, and low septal right atrial electrograms followed the onset of QRS complexes by 85, 105, 150, and 175 ms, respectively), and the atria could be reset by ventricular extrastimuli introduced when the His bundle was being depolarised anterogradely, suggesting that this tachycardia reflected a circus movement using the anomalous pathway as the retrograde limb.[1] The AH interval was relatively long (130 ms), suggesting that the anterograde limb of the circus movement was the slow atrioventricular nodal pathway (see Discussion).

Tachycardia No.1 (induced only once, by ventricular pacing) was characterised by functional left bundle-branch block and a stable cycle length of 330 ms. The sequence of atrial activation during this tachycardia was identical to the sequence observed during tachycardia No.2, suggesting that tachycardia No.1 also reflected a circus movement which used the anomalous pathway as the retrograde limb. During this tachycardia, the AH interval was very short (30 ms), suggesting that the anterograde limb of the circus movement was the fast atrioventricular nodal pathway (see Discussion).

During tachycardia No.1 paroxysmal loss of functional left bundle-branch block resulted in tachycardia No.2 (Fig.). This loss of bundle-branch block caused shortening of the intervals from onset of QRS complexes to each of the atrial electrograms by 75 ms (from 160 to 85 ms for the distal coronary sinus electrogram). The cycle length of tachycardia, however, did not shorten but lengthened by 25 ms. The lengthening of the tachycardia cycle length reflected an increment in AH interval of 100 ms (from 30 to 130 ms) which more than compensated for the decrement

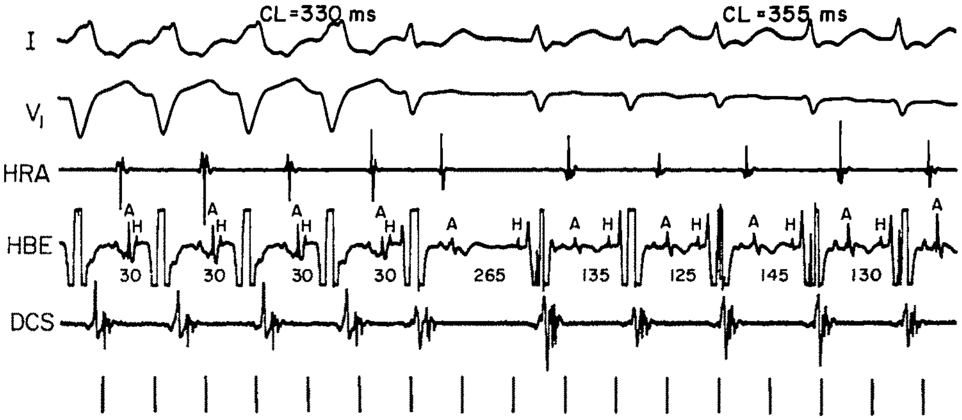

Fig. *Paroxysmal loss of functional left bundle-branch block during atrioventricular re-entrant tachycardia. Electrocardiographic leads I and VI, as well as high right atrial (HRA), His bundle (HBE), and distal coronary sinus (DCS) electrograms, are shown. AH intervals are shown below HBE. Time lines (bottom) are at 200 ms intervals. The first four beats of re-entrant tachycardia are conducted with left bundle-branch block and have cycle length (CL) 330 ms. Note that the sequence of retrograde atrial activation is eccentric, proceeding from DCS to HRA and then to the low septal right atrium (HBE), and that the AH interval is 30 ms (fast atrioventricular nodal pathway conduction). At the fifth beat there is sudden loss of left bundle-branch block, resulting in shortening of the ventriculoatrial interval. The tachycardia continues, with the last five beats of paroxysmal supraventricular tachycardia being conducted normally and having CL 355 ms. Note that the sequence of retrograde atrial activation is unchanged, but that the AH interval is 130 ms (slow atrioventricular nodal pathway conduction).*

in ventriculoatrial interval. The HV interval was 50 ms during each of the tachycardias.

Discussion

Occasional patients have dual atrioventricular pathways coexisting with anomalous atrioventricular pathways.[5 6] These patients have the potential for several distinct circus movement tachycardias.[5 6] Our patient had anterograde dual atrioventricular nodal pathways, and a concealed left-sided anomalous atrioventricular pathway which was used as the retrograde limb of two circus movements. One circus movement used the slow atrioventricular nodal pathway (AH intervals of 130 ms) as the anterograde limb, and was conducted with normal QRS complexes. The other circus movement used the fast atrioventricular nodal pathway (AH intervals of 30 ms) as the anterograde limb, and was conducted with left bundle-branch block. Fast and slow pathway AH intervals were shorter during these circus movements than during high right atrial pacing. This probably reflected the fact that during these circus movements input to the atrioventricular node was from the left atrium, as AH intervals are significantly shorter during coronary sinus pacing than during high right pacing at equivalent rates.[7]

Our patient presented an almost unique finding. During induced atrioventricular re-entrant tachycardia, paroxysmal loss of functional bundle-branch block resulted in sudden lengthening of the cycle length of tachycardia. The explanation for this finding is as follows. When the functional bundle-branch block was lost, the ventriculoatrial interval shortened, resulting in early atrial depolarisation and early anterograde input into the atrioventricular node. This early input found the fast atrioventricular nodal pathway refractory, and conducted anterogradely over the slow atrioventricular nodal pathway. Subsequent beats of the narrow QRS tachycardia also conducted over the slow pathway, probably because of retrograde concealment into the fast pathway. The cycle length of tachycardia increased because the increment in AH interval (slow pathway instead of fast pathway conduction) more than compensated for the decrement in ventriculoatrial interval (narrow QRS instead of left bundle-branch block).

We are aware of only one patient similar to ours. Akhtar and co-workers[8] reported a patient with induced atrioventricular re-entrant tachycardia, during which loss of functional right bundle-branch block resulted in a 20 ms increase in cycle length of tachycardia, because the AH interval increased by 65 ms whereas the ventriculoatrial interval decreased by only 45 ms. An explanation for this observation was not given. We suspect that their patient had anterograde dual atrioventricular nodal pathways, which were not shown during atrial extrastimulus testing because the fast pathway effective refractory period was shorter than the atrial functional refractory period at the cycle length employed.

Our observations provide an additional surface electrocardiographic clue to the diagnosis of a specific mechanism of paroxysmal supraventricular tachycardia. Slowing of tachycardia with loss of functional bundle-branch block (or speeding of tachycardia with the occurrence of functional bundle-branch block) suggests the possibility of anterograde dual atrioventricular nodal pathways coexisting with an anomalous atrioventricular pathway ipsilateral to the site of functional bundle-branch block.

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Br Heart J 1982; **48**: 78–80

Presystolic mitral closure sound in aortic regurgitation with left ventricular hypertrophy and first degree heart block

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SUMMARY We report a patient who developed aortic regurgitation and first degree atrioventricular block caused by infective endocarditis complicating aortic valve stenosis. There was premature closure of the mitral valve and, in the absence of an Austin Flint murmur, a simultaneous high frequency sound was audible which we regard as a presystolic first heart sound. That such a sound may be associated with valve closure, even though this precedes electrical and mechanical ventricular systole, provides further support for the valvular origin of the first heart sound.

It is generally taught that the two components of the first heart sound are the result of closure of the mitral and tricuspid valves. An alternative mechanism has been proposed, however, which relates the audible sounds to left ventricular myocardial contraction and the onset of ejection.[1] Because the events in question usually occur within a short time of one another, neither hypothesis has received conclusive support, so that circumstances in which atrioventricular valve closure is dissociated from the onset of ventricular systole might provide an opportunity to distinguish these possibilities. In cases of aortic regurgitation the left ventricular diastolic pressure may exceed the left atrial pressure so that the mitral valve closes before the onset of contraction. In such patients the sound which follows the QRS is soft, but a distinct premature mitral valve closing sound is not usually heard. We report a patient who had left ventricular hypertrophy, first degree atrioventricular block, and aortic regurgitation, in whom premature mitral valve closure was associated with an audible diastolic heart sound.

Case report

A 78-year-old black man was admitted for investigation of a cerebrovascular accident. Two years previously he had developed shortness of breath and angina pectoris, and was found to have aortic valve stenosis. He was treated with digoxin and diuretics which improved his symptoms. Two months before the present admission he began to feel generally unwell and developed anorexia, weight loss, nocturnal dyspnoea, and night sweats. The night before admission he experienced abrupt onset of right sided weakness and difficulty with speech.

There were signs of recent weight loss, a fever, and mild right sided spastic paresis. There were no peripheral stigmata of infective endocarditis. The heart rate was 84 per minute and blood pressure 110/60 mmHg. Peripheral pulses were of small volume and there was a carotid thrill. There were no signs of fluid retention. The cardiac impulse was felt in the sixth interspace at the anterior axillary line and was sustained. On auscultation both first and second heart sounds were soft. A loud ejection systolic murmur was heard at the base, and there was a soft early diastolic murmur. There were two added sounds in diastole. The first of these was soft and of low frequency; this was followed by a second, louder, and of high frequency.

The electrocardiogram showed sinus rhythm with first degree atrioventricular block and left ventricular hypertrophy. The echocardiogram showed severe left ventricular hypertrophy with reduced end-systolic and end-diastolic dimensions. There was premature closure of the mitral valve. Simultaneous recording of the apexcardiogram, phonocardiogram, and echocardiogram (Fig.) indicated that of the two added sounds in diastole, the first low frequency sound coincided with a combined rapid filling wave and a-wave of the apical impulse, and thus represented a summation sound. The second high frequency one coincided with presystolic mitral valve closure.

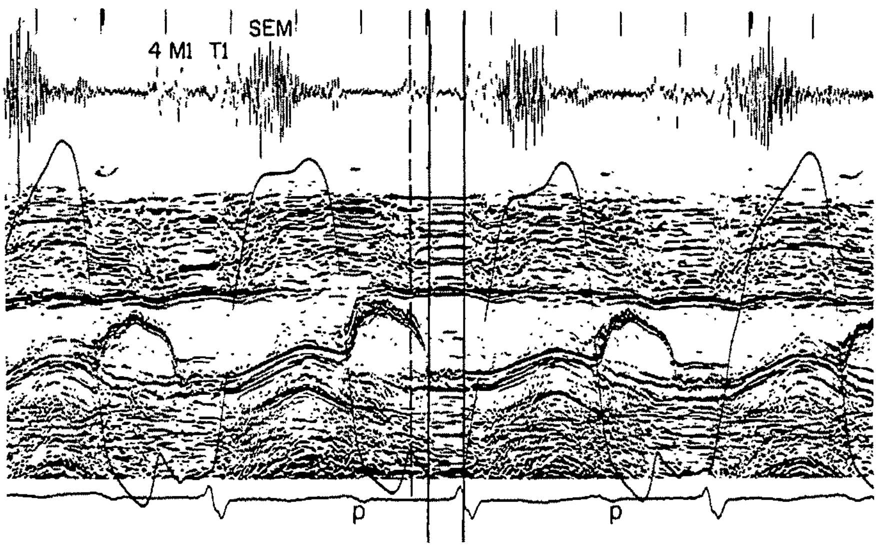

Fig. *Simultaneous recording of phonocardiogram, echocardiogram, apexcardiogram, and electrocardiogram. Following the P wave (P) a combined rapid filling wave and a-wave is evident in the apexcardiogram, synchronous with the sound labelled 4. Apposition of the mitral valve leaflets coincides with the sound labelled M1. T1, tricuspid component of the first sound; SEM, systolic ejection murmur.*

Blood cultures grew *Strep. viridans* and the patient was treated with a course of parenteral penicillin and gentamicin. His neurological changes improved and he was discharged after six weeks, taking digoxin and hydrochlorothiazide.

Discussion

The subject of the present report had left ventricular hypertrophy and first degree atrioventricular block together with aortic regurgitation which was of recent onset but not severe. The echocardiogram shows complete mid-diastolic closure of the mitral valve, which was accompanied by an easily audible high frequency sound. This followed by some 200 ms a low frequency sound which, from its relation to the combined rapid filling wave and a-wave of the apexcardiogram, we take to be a summation sound. Both the timing of these sounds, and their relative frequencies, make us conclude that the second is a true mitral closure sound and thus represents a presystolic "first heart sound". Following the onset of the QRS by 45 ms there occurred a further high frequency sound, which was not split, and which preceded the onset of ejection as evidenced by the carotid upstroke. This we take to represent the second component of the first heart sound, and presumably corresponds to tricuspid valve closure.

Premature closure of the mitral valve and the loud sound which accompanied it were probably the result of a combination of factors. In patients with acute or severe aortic regurgitation the mitral valve frequently closes before the onset of left ventricular systole. This was at first inferred from the observation of diastolic crossover of the left ventricular and left atrial pressures[2-5] and has since been confirmed by a number of echocardiographic studies.[6-9] Such premature closure has been identified as part of the mechanism of the Austin Flint murmur.[7] Though it has been noted that the first heart sound is attenuated in such patients, in only one report has mention been made of a diastolic sound and this was recorded with an intracardiac microphone.[5] Meadows *et al.*[10] considered the possibility that a mid-diastolic mitral valve closure sound in their patients might have been masked by the presence of an Austin Flint murmur. In uncomplicated first degree heart block, when the first heart sound is audible it follows the onset of ventricular systole. Its intensity appears to depend on the degree of separation of the mitral leaflets at end-diastole, in turn determined by the interval between the atrial and ventricular contributions to mitral valve closure. When apparent presystolic closure of the valve occurs, this is not usually audible or recordable.[11] We speculate that in the present patient the simultaneous occurrence of rapid filling and atrial systole coupled with persisting retrograde filling of the ventricle caused an abrupt rise in ventricular diastolic pressure and sudden termination of forward flow across the mitral valve. The signs did not suggest that aortic regurgitation was itself of great severity and the patient did not require surgery, so that the rapid rise in ventricular diastolic pressure must be attributable more to its abnormal elasticity than to the magnitude of the diastolic volume load.

The arguments for the valvular hypothesis of the generation of the first heart sound are based for the most part on the simultaneous occurrence of the two components with the corresponding movements of the mitral and tricuspid valves, studied indirectly by manometry[1] or more directly by echocardiography.[12] Thus mitral valve closure has been shown to occur an appreciable interval after the crossover of left atrial and left ventricular pressures, and synchronous with the first component.[13] Similarly, the second component precedes aortic valve opening, and is synchronous with tricuspid valve closure, a relation that persists when tricuspid closure is delayed.[14] Further evidence for the valvular hypothesis is the finding that in atrioventricular block the intensity of the first sound varies according to the velocity of closure of the mitral valve leaflets.[11] In all such studies, however, it is impossible to separate the timing of valve movements from the other mechanical events that characterise the onset of left ventricular systole, so that effects of the latter can never be completely discounted as contributing to the audible sound. The occurrence of premature mitral valve closure in cases of aortic regurgitation with high left ventricular diastolic pressure therefore provides an experiment of nature in which valve movements and ventricular systole are dissociated. Our finding that in this situation the first component of the first heart sound may also be dissociated from ventricular systole seems to us to lend further support to the valvular hypothesis.

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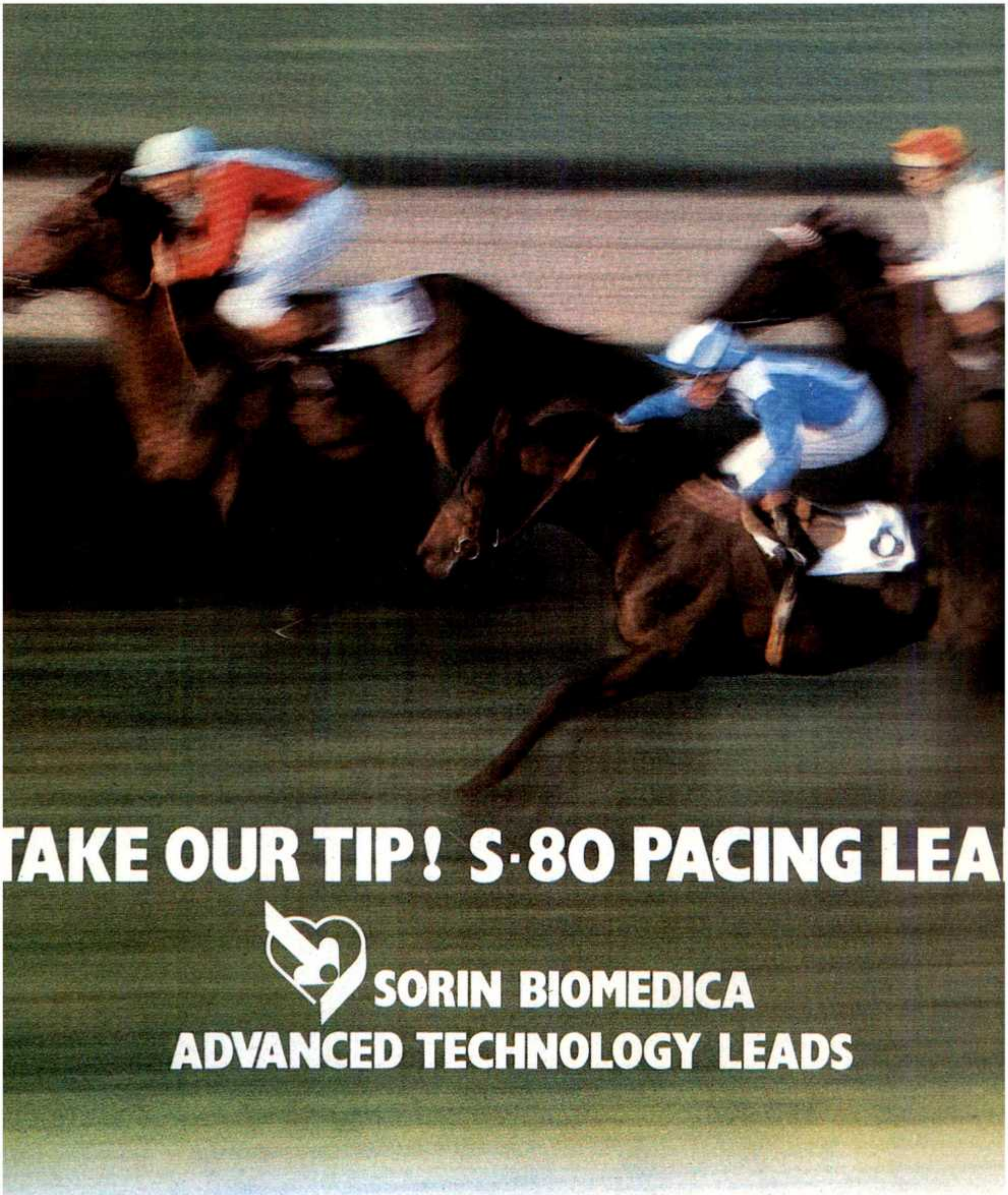

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Br Heart J 1982; **48:** 81–2

Coronary artery surgery using inverted internal mammary artery

J J GOITI, G H SMITH

From the Cardiothoracic Unit, Northern General Hospital, Sheffield

SUMMARY A 56-year-old man requiring multiple coronary artery bypass grafts but without enough suitable vein was operated upon using the retrograde flow of the right internal mammary artery to supply the posterior descending coronary artery.

Relief of angina and non-ischaemic areas on the scan with thallium-201 supports our intention to use this method when other techniques are not possible.

Coronary artery bypass using autologous venous grafts is established in the treatment of angina pectoris. Daunting technical problems are encountered when no suitable veins are available.

The purpose of reporting this case is to present the clinical use of retrograde internal mammary artery grafting to overcome this problem.

Case report

A 56-year-old journalist was known to suffer with mild diabetes mellitus and to have Fredrickson type IV hyperlipidaemia. He had two previous myocardial infarctions. He complained of severe angina unresponsive to conventional medical treatment. In the past he had suffered with varicose veins in both legs and had had deep venous thromboses. In addition, the veins in the arms had been damaged by multiple injections and infusions during the treatment of diabetic complications.

Coronary arteriography showed a 90% stenosis of the left anterior descending coronary artery, involving the origin of the first diagonal coronary artery, 70% stenosis at the origin of the obtuse marginal artery, and total occlusion of the right coronary artery in its middle third. The distal right coronary artery filled retrogradely from the left-sided injection.

Surgery was performed on 30 March 1981. In spite of multiple explorations, only enough vein for one graft, of about 12 cm, could be found. After median sternotomy, both internal mammary arteries were mobilised from the second to the seventh costal cartilage. The left-sided artery was divided at the level of the diaphragm and excellent anterograde flow was obtained. The right internal mammary artery was divided at the level of the second costal cartilage and a retrograde flow of approximately 40 ml/min was obtained.

After cardiopulmonary bypass was established, cold cardioplegic solution arrested the heart. The vein was sewn to the opened obtuse marginal artery which

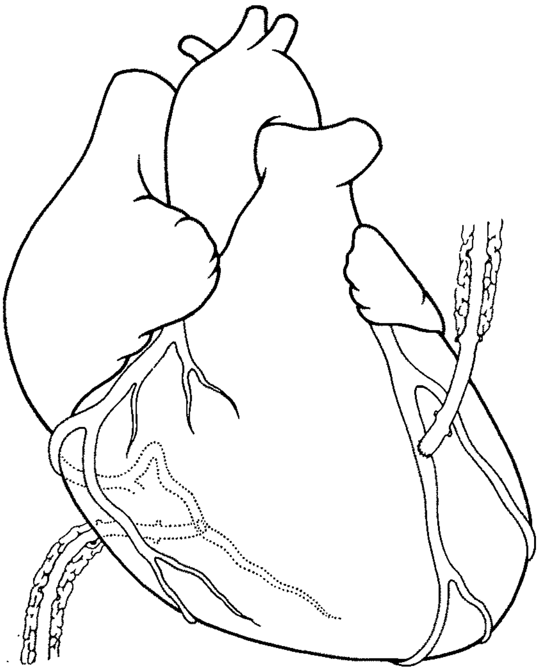

Fig. *Left internal mammary artery anastomosed to the left anterior descending coronary artery. Retrograde right internal mammary artery anastomosed to posterior descending coronary artery. Vein graft to the obtuse marginal and first diagonal are not shown.*

had a lumen of 2 mm and a side to side anastomosis was performed to the first diagonal artery which had a lumen of 1·5 mm. The left internal mammary artery was anastomosed to the left anterior descending coronary artery (2 mm) and the retrograde right internal mammary to the posterior descending coronary artery (2 mm). The venous anastomoses were performed using 6/0 Prolene and the mammary arterial anastomoses with 7/0 Prolene.

Spontaneous defibrillation occurred on removal of the aortic clamp at 50 minutes. The vein was attached to the ascending aorta.

The period after bypass and after the operative period was uneventful. Examination of the electrocardiogram and serum enzymes showed no evidence of myocardial damage.

Eighteen days after operation the patient had myocardial imaging using thallium-201. Exercise to exhaustion did not cause angina. The scan showed a defect of distribution without later correction in the lateral wall of the left ventricle only, suggesting lateral myocardial infarction, compatible with the history before operation. Angiography showed excellent patency of the left internal mammary artery graft, but occlusion of the venous graft. Repeated attempts to inject the right internal mammary artery via the epigastric route failed.

The patient continues to be free of pain and is leading a very active life eight months after operation.

Discussion

Our experience with artificial substitutes for coronary artery bypass graft in the absence of autologous vein has been far from satisfactory. This patient who required four coronary artery bypass grafts forced us to adopt the above manoeuvre, having read the experimental results of Folts *et al.*[1] using retrograde internal mammary artery flow for revascularisation of coronary arteries. We believe this is the first clinical use of this method.

The patency rate of internal mammary arteries is higher than autologous vein grafts, but only with anterograde flow.[2] Unfortunately, we have not been able to show the patency of the graft by angiography because of anatomical difficulties, but the thallium scan suggests good myocardial perfusion in the area perfused by the retrograde right internal mammary artery graft. In addition, angiography after operation did not show retrograde filling of the right coronary artery, as happened before operation, though of course this could be the result of operative damage to the artery. The total relief of the angina in this patient supports the idea of using this new technique in cases requiring multiple coronary artery bypass grafts when other techniques are inappropriate.

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Br Heart J 1982; **48:** 83–4

Reliability and clinical relevance of detection of vegetations by echocardiography in bacterial endocarditis

Sir,
The recent paper by Hickey *et al.* (*Br Heart J* 1981; **46:** 624–8) provides an interesting indication of the potential use of M-mode echocardiography in patients with infective endocarditis.

In view of their findings, the criteria for differentiating the echocardiographic appearances of vegetations from those of the underlying valve disease are clearly important. For instance, chordal rupture associated with mitral valve prolapse can result in echocardiographic patterns which resemble those produced by "shaggy non-uniform masses". By contrast, the presence of heavy calcification of valve cusps often prevents recognition of more subtle associated structural abnormalities. In the presence of heavy calcification or rheumatic disease causing restriction of leaflet motion were the authors able to detect vegetations around the valves themselves, or were the vegetations only detectable in the left atrium or left ventricular outflow tract?

Peter Mills,
The London Hospital,
London E1.

This letter was shown to Drs Hickey, Wolfers, and Wilcken who reply as follows.

Sir,
We thank Dr Mills for his comments about our paper and for drawing attention to the two important groups of patients in whom the diagnosis of vegetations by echocardiography may prove difficult—those with thickened or calcified valves and those with mitral valve prolapse and chordal rupture.

In relation to the first problem, we have made a definite diagnosis of vegetations in thickened or calcified valves when vegetations were identified in the left atrium or left ventricular outflow tract (as Dr Mills mentions), when vegetations were detected in a valve other than one thickened, that is vegetations on a normal mitral valve with a thickened and presumably affected aortic valve, or when sequential echocardiograms obtained over several weeks revealed progressive changes. We stress the importance of sequential echocardiograms. Thus, in our study there were seven patients with thickened aortic valves and one with mitral stenosis in whom vegetations were considered to be present. Of the patients with aortic valve disease, two had vegetations visible in the ventricular outflow tract, as shown in Fig. 1 of our paper, and three had progressive changes in and around the aortic valve leaflets over periods ranging from six to eight weeks; the remaining two patients with thickened aortic valves had vegetations on their mitral valves and there was confirmation of bivalvular involvement in one (necropsy was refused in the other). In the one patient with mitral stenosis, shaggy echoes were noted both in systole and diastole around the thickened mitral leaflets. A diagnosis of probable vegetations only was made in this case, with subsequent confirmation at surgery.

We certainly agree with Dr Mills that there is a risk of making a false positive diagnosis of vegetations in patients with chordal rupture complicating mitral valve prolapse. There were six patients in our study with clearly defined mitral valve prolapse at echocardiography. Only one of these was considered to have vegetations (Fig. 2 of our paper) and these were found at surgery. None had evidence of chordal rupture. Since the completion of our study, however, we have had a patient with *Streptococcus viridans* endocarditis on a floppy mitral valve with chordal rupture. We did not consider this patient had vegetations on the M-mode study using our criteria, but we made a confident diagnosis of vegetations on the basis of a two dimensional study which appeared to show a large vegetation attached to the tip of the anterior leaflet. At surgery after six weeks of chemotherapy there was microscopical evidence of infection in the excised valve, ruptured chordae to the anterior leaflet, but no detectable vegetations. After viewing the specimen we did not see how one could have differentiated the mass we detected, which was the flail myxomatous tip of the anterior leaflet, from vegetations. Perhaps, however, the distinction is not crucial to the management in a patient with suspected or proven infective endocarditis receiving appropriate antibiotic treatment since early surgery is usually indicated for chordal rupture anyway.

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Australia.

Correspondence

Br Heart J 1982; **48:** 85–6

Electrocardiogram of pure left ventricular hypertrophy and its differentiation from lateral ischaemia

Sir,

I was delighted to read Beach, Kenmure, and Short's paper[1] emphasising features of the final ventricular configuration (repolarisation) that distinguishes left ventricular hypertrophy from myocardial ischaemia. Credit, however, should have been given to the pioneers who first described them.

Pardee[2] first pointed out the configuration of the T waves which are characteristic of myocardial infarction. These T waves were subsequently called Pardee waves or coronary T waves. I was taught these findings during my junior year by Herrick who was still giving an occasional lecture at that time. Pardee quoted Herrick's famous case,[3] the first clinical example of a coronary T wave. At Herrick's suggestion, Smith[4–6] ligated coronary arteries in dogs and was able to demonstrate typical coronary T waves.

Barnes and Whitten[7] were the first to describe in detail the T wave configuration in predominant ventricular hypertrophy, which they called strain. They acknowledged the influence of Willius, their colleague at the Mayo Clinic, and also Wilson's concept of the ventricular gradient. Wilson objected to the word strain because it is not an electrical term. Barnes re-emphasised these findings and the differentiation from those of ischaemia in his monograph on electrocardiographic patterns.[8] The T wave findings in left ventricular hypertrophy appeared in Ashman and Hull's elementary[9] and in Sodi-Pollares and Calder's advanced textbook on electrocardiography.[10] Emphasis was placed upon the depression of the ST segment even when it was as little as 0·5 mm, the asymmetric T wave, and the low and flat T wave. Goldberger[11] noted the appearance of a roller-coaster effect with downward T waves terminating above the baseline.

The differentiation between the configuration of repolarisation caused by myocardial ischaemia from that of left ventricular hypertrophy is clearly described in the books by Katz[12] and by Sodi-Pollares and Calder.[10]

This distinction of course is not absolute because of the occasional simultaneous presence of both lesions and because of the superimposed effects of drugs (digitalis) or electrolyte abnormalities; there may also be a problem if the electrocardiogram is taken soon after the ingestion of a high carbohydrate diet, after an injection of insulin, or immediately after physical activity.

Beach *et al.*[1] correctly state that QS complexes in the right precordial leads are not diagnostic of an infarction. They may occur, as they state, in isolated left ventricular hypertrophy and may also occur in infiltrative disorders of the myocardium (amyloidosis, tumours) frequently when the leaves of the diaphragm are depressed (emphysema), in right atrial enlargement (tricuspid regurgitation), and, rarely, in normal individuals when there is pronounced clockwise rotation of the electrical axis. If the electrodes are erroneously placed too high on the thoracic wall, which is a not uncommon error in women with large breasts, QS complexes may be seen.

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This letter was shown to Drs Beach, Kenmure, and Short who reply as follows:

Sir,
We are grateful to Dr Soloff for reminding us of observations on the repolarisation pattern in left ventricular hypertrophy made by earlier workers in this field. We have reviewed most of the publications to which Dr Soloff refers. It is true that ST depression, T wave asymmetry, and a "roller-coaster" pattern are described. Nevertheless, the descriptions are confused and conflicting, and we found no evidence of any attempt to quantify the degree of asymmetry in left ventricular hypertrophy to enable this to be used to discriminate between hypertrophy and ischaemia.

It is therefore not surprising that the idea that there might be definable differences between the pattern of repolarisation in left ventricular hypertrophy and that in coronary disease was never established. We do not know of a single textbook on electrocardiography, published in the past 20 years, which draws attention to these differences; indeed most state or imply that the patterns are indistinguishable.

Early workers were limited by the fact that they were not able to exclude the coexistence of coronary narrowing along with left ventricular hypertrophy except at necropsy. It is now possible to do this during life; so we have a secure basis for comparing the electrocardiography of "pure" left ventricular hypertrophy with that of coronary heart disease.

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Proceedings of the British Cardiac Society

THE 61ST ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Medical School in the Queen's Medical Centre at Nottingham University on Wednesday and Thursday 14 and 15 April 1982. The President, M F OLIVER, took the Chair during private business. At the scientific sessions the Chair was taken by J R HAMPTON.

Abstracts of papers

Direct electrophysiological effects of disopyramide phosphate—evaluated in denervated human heart

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In order to evaluate the direct intrinsic effects of intravenous disopyramide phosphate (2 mg/kg), the drug was administered to eight orthotopic cardiac transplant recipients undergoing electrophysiological study.

The sinus cycle length of the denervated donor right atrium was significantly increased by disopyramide (626±53 ms to 716±60 ms, $p<0{\cdot}001$) while that of the innervated recipient right atrium decreased (846±80 ms to 659±41 ms, $p<0{\cdot}02$). The AH interval (55±5 ms to 78±5 ms, $p<0{\cdot}001$), HV interval (38±3 ms to 58±5 ms, $p<0{\cdot}001$), QRS duration (93±7 ms to 129±13 ms, $p<0{\cdot}001$), QT interval (339±9 ms to 403±15 ms, $p<0{\cdot}001$), and QTc (435±11 ms to 487±10 ms, $p<0{\cdot}01$) measured during sinus rhythm were all very prolonged.

The sinus node recovery time (1128±252 ms to 1198±242 ms, $p<0{\cdot}05$) and corrected sinus node recovery time (440±171 ms to 489±167 ms, $p<0{\cdot}02$) of the denervated donor atrium were significantly prolonged by disopyramide whereas the recovery times of the innervated recipient atrium shortened slightly. During incremental pacing the atrioventricular Wenckebach cycle length (314±8 ms to 350±13 ms, $p<0{\cdot}01$) increased after disopyramide, as did the ventricular arterial Wenckebach cycle length (419±62 ms to 500±61 ms, $p<0{\cdot}01$). The drug had no effect on the effective refractory period of the atrium, atrioventricular node, or ventricle though the functional refractory period of the atrioventricular node was prolonged (369±13 ms to 395±12 ms, $p<0{\cdot}001$).

In comparison with effects on the innervated normal heart, the direct intrinsic effects of disopyramide on the transplanted denervated heart are conspicuously depressant.

Prognosis of chronic second degree atrioventricular block

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This paper presents the findings of the prospective follow-up of patients with second degree block seen in the Devon Heart Block and Bradycardia Survey started in 1968. Patients with conduction disturbance which occurred within 28 days of myocardial infarction or pericarditis are excluded, as are those with drug-induced block. Two hundred and seventy patients with second degree block have been seen in the survey; in 44 instances evidence of higher degree of block was available leaving 226 patients presenting with second degree block. The patients were divided into Mobitz I and Mobitz II groups according to the usual criteria, the mean age of the former group being four years less than the latter.

Temporary or sustained improvement in conduction was seen in 20% of patients and 46% progressed to third degree block. The five year survival for the whole group was approximately 50% and surprisingly it was similar for both of the Mobitz groups. Paced patients faced significantly better than unpaced, this difference being maintained even when corrected for age.

Comparative electrophysiological effects of novel antiarrhythmic drug, bepridil

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Bepridil is a novel, non-iodinated, fast and slow channel blocker that prolongs myocardial refractoriness and depresses atrioventricular nodal function. We compared intravenous bepridil (2·0 mg/kg) with verapamil (0·15 mg/kg) in nine patients with reciprocating atrioventricular nodal tachycardia, and with ajmaline (0·75 mg/kg) in eight patients in whom re-entry tachycardia was associated with the Wolff-Parkinson-White syndrome; 12 of these patients were restudied three days after oral bepridil (1500 mg) when steady state had been achieved. Intravenous bepridil increased sinus cycle length in all patients (40 to 120 ms, mean 66) and increased the AH interval (0 to 20 ms, mean 8). No effect was seen on His-Purkinje conduction. The "pre-Wenckebach cycle length" of the atrioventricular node was prolonged after bepridil (45 to 150 ms, mean 95) as were the effective refractory periods of the atrioventricular node (50 to 90 ms, mean 74), atrium (10 to 50 ms, mean 28), ventricle (0 to 30 ms, mean 14), and accessory pathway retrograde (55 to 70 ms, mean 63). Tachycardia terminated in all patients after verapamil or ajmaline whereas failure occurred in three patients after bepridil: all had pre-excitation. At restudy after oral bepridil reinitiation was impossible in six patients; in the other six tachycardia was slower, and terminated spontaneously (two) or with single stimuli.

Bepridil thus possesses a combination of electrophysiological properties, each of its actions comparable to representative conventional agents: this broad spectrum of antiarrhythmic action ia appropriate for the safe and effective treatment of supraventricular arrhythmias.

Electrophysiological effects of sotalol—more than just another beta blocker

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The electrophysiological effects of intravenous sotalol hydrochloride (0·4 mg/kg) were assessed in 24 patients, including 13 with the Wolff-Parkinson-White syndrome. Fifteen minutes after sotalol administration there was an increase in sinus cycle length (739±107 to 869±109 ms, $p<0·001$) and in sinus node recovery time (1084±302 to 1270±301 ms, $p<0·01$). The AH interval increased (82±28 to 94±32 ms, $p<0·001$), but the HV interval was unchanged. The QRS duration was also unchanged, but the QT (401±45 to 427±38 ms, $p<0·01$) and the JT (300±44 to 321±35 ms, $p<0·02$) intervals were both increased. The atrial (216±38 to 233±40 ms, $p<0·01$), ventricular (231±30 to 242±31 ms, $p<0·01$), and atrioventricular nodal (294±87 to 338±90 ms, $p<0·001$) effective refractory periods were all prolonged, as was the atrioventricular nodal functional refractory period (417±92 to 467±86 ms, $p<0·001$). In the 13 patients with ventricular pre-excitation there was an increase in the accessory pathway anterograde (317±88 to 350±81 ms, $p<0·02$) and retrograde (296±40 to 371±139 ms, $p<0·05$) effective refractory periods. In 12 of these 13 sotalol was given during atrioventricular re-entrant tachycardia, resulting in termination in five. Tachycardia cycle length increased in all patients (355±64 to 413±54 ms, $p<0·001$) with the major effect being in the atrioventricular direction (atrioventricular interval 230±69 to 286±54 ms, $p<0·001$). The effect on atrial, ventricular, and accessory pathway effective refractory periods and on ventricular repolarisation is not typical of that observed with other beta blockers but may be the result of lengthening of the action potential duration, as seen with amiodarone. These findings suggest that sotalol may be more versatile than other beta receptor antagonists in the treatment of arrhythmias.

Ventricular arrhythmia in tetralogy of Fallot: influence of age, haemodynamic factors, and surgery

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Serious ventricular arrhythmia occurs after correction of tetralogy of Fallot and may be associated with late sudden death. To determine the factors responsible for these arrhythmias, we studied 38 unoperated patients (age 2 months to 45 years) and 77 postoperative patients (follow-up three to 22, mean 14·6 years) using 48 hour electrocardiographic monitoring. Thirty-one of the postoperative patients had cardiac catheterisation and gated equilibrium radionuclide angiography using Krypton-81m (right ventricle) and technetium-99m (left ventricle), at rest and after isometric exercise. None of the unoperated patients aged below 9 years had significant arrhythmia. Four of seven patients older than 10, however, had ventricular arrhythmia, of whom three had ventricular tachycardia. No other clinical or haemodynamic measurements distinguished these patients. Thirty-three postoperative patients (43%) had serious ventricular arrhythmia and four (5%) ventricular tachycardia. There was no significant difference in haemodynamic status or ventricular ejection fraction between patients with ventricular arrhythmia and those without. Ventricular arrhythmia was significantly more frequent in those operated on at an older age. (One of 14 aged 2 to 7, 19 of 45 aged 8 to 15, 13 of 18 aged 16 or more; $p<0{\cdot}01$).

Thus, ventricular arrhythmias cannot be predicted from the postoperative haemodynamic status of the patient. They are related to the timing of correction rather than to the operation itself.

Increased atrial pacing threshold in heart transplant rejection

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The pacing threshold of the donor right atrium was measured in eight heart transplant recipients for 27 to 46 days (mean 33) after transplantation. Threshold current and potential were measured at nine different pulse widths each day during the period of study and correlated with the degree of rejection diagnosed by right ventricular endomyocardial biopsy. Biopsies were performed each seven to 10 days or on suspicion of rejection. Histological grading was from 0 (normal) to 4 (severe rejection). The degree of rejection was correlated with the mean values of current, potential, power, and energy on the day of the biopsy. There were insufficient examples of grade 1 and grade 4 rejection for statistical analysis (paired Student's t test).

During rejection there was significant increase in potential ($p<0{\cdot}02$), current, power, and energy ($p<0{\cdot}01$) compared with the values associated with normal biopsies. The values associated with grade 2 and grade 3 rejection were not significantly different. Similar results were obtained with all pulse widths.

Right atrial pacing threshold correlates well with rejection of the transplanted heart but does not indicate the severity of rejection.

Haemodynamic and metabolic effects of diltiazem, a new calcium antagonist, compared with nifedipine in patients with coronary artery disease

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Diltiazem is a new calcium channel blocking agent which may have value in patients with angina pectoris. The haemodynamic and myocardial metabolic effects of diltiazem have been compared with those of nifedipine at rest and during rapid atrial pacing in 20 patients with obstructive coronary artery disease. No patient was receiving a beta blocking agent at the time of the study.

Diltiazem, 0·25 mg/kg intravenously given over two minutes followed by 0·005 mg/kg per min, produced a fall in systemic vascular resistance from 20·1 to 15·7 units ($p<0{\cdot}002$) with an increase in cardiac output from 5·5 to 6·5 l/min ($p<0{\cdot}01$) and a fall in mean arterial pressure from 100 to 92 mmHg ($p<0{\cdot}005$). Coronary sinus blood flow rose after both drugs. Comparable haemodynamic changes occurred after nifedipine 20 mg sublingually. The systemic vasodilator effects of diltiazem, however, were not associated with a change in resting heart rate, whereas after nifedipine it rose from 70 to 80 beats/min ($p<0{\cdot}001$).

Importantly, after diltiazem, mean pacing time to angina increased from 174 to 356 seconds ($p<0{\cdot}02$) and mean lactate extraction improved from −22% (ie production) to +2%. The atrial pacing time to angina and the myocardial lactate extraction ratio after nifedipine did not change significantly.

The effects of diltiazem differ importantly from those of nifedipine and may be advantageous in the treatment of angina pectoris.

Comparison of "dipyridamole-exercise" thallium-201 imaging and standard exercise thallium-201 imaging in men with angina

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Traditional thallium-201 myocardial imaging as performed with exercise or dipyridamole stress. We have devised a method for combining oral dipyridamole and treadmill exercise in one test: "dip-ex" testing. In 13 men with angina this was a more effective stress than exercise alone.

Thirteen men with mild to moderate angina and good exercise performance were selected. In seven, coronary artery disease had been demonstrated angiographically; in the remaining six, in whom angiography was inappropriate, the presence of coronary artery disease was accepted on the typical history combined with an ischaemic exercise electrocardiogram. (The prevalence of coronary artery disease in such men is 96 to 100%.)

Patients underwent thallium-201 imaging on two occasions, two weeks apart. On one occasion, dipyridamole 300 mg was taken by mouth 60 minutes before exercise. Thallium-201 2 mCi was given intravenously at maximal exercise.

Thallium-201 imaging was abnormal (regional count deficit of >25%) in 12 patients after dip-ex testing and in eight after exercise alone. Dip-ex testing disclosed a total of 26 abnormal myocardial regions in the 13 patients, while exercise imaging showed 12. When only the dip-ex images were abnormal, angiography tended to show at least one occluded or critically narrowed vessel, and a well developed collateral circulation.

The mean myocardial to background ratio was 3·48±0·75 after dip-ex testing and 2·95±0·55 after exercise alone ($p<0·01$).

The dip-ex technique has now been used diagnostically in 60 patients. It is useful, simple, and safe.

Relation between episodes of reversible cardiac ischaemia and arrhythmias

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Cardiac arrhythmia is the presumed predominant cause of sudden death in patients with ischaemic heart disease; however, the precise relation between acute ischaemic episodes and cardiac arrhythmias in such patients is uncertain.

To examine this relation, 40 patients with angina caused by coronary artery disease were studied with continuous 24 hour electrocardiographic FM recordings, 28 of whom also had stress electrocardiograms that were analysed for *both* ischaemic and *arrhythmic* events. Only two patients (5%) had symptoms of cardiac arrhythmia. Patients with acute myocardial infarction within two weeks were excluded.

Twenty-six of 40 24 hour electrocardiograph tapes (65%) showed ischaemic episodes characterised by 1·5 mm or greater ST segment depression or elevation 0·08 s after the J point. Thirty-seven (92·5%) of these same tapes showed cardiac arrhythmias. Arrhythmias were immediately associated with episodes of ischaemia in six patients (16·2% of tapes showing arrhythmia, 15% total tapes); ischaemia precipitated arrhythmia in five (19·2% of tapes showing ischaemic episodes, 12·5% total tapes), and vice versa in one (2·7% of tapes showing arrhythmia, 2·5% total tapes). Of nine arrhythmias precipitated by ischaemia, two were ventricular tachycardia, two complex or early ventricular extrasystoles, three simple ventricular extrasystoles, and two conduction disturbances. Apparently similar episodes of ischaemia in the same patient did not consistently reproduce the cardiac arrhythmia. There was no significant difference in arrhythmias produced by either "demand" or "spontaneous" ischaemia but the incidence was greater with severe and prolonged ischaemia. Exercise testing produced angina and/or electrocardiographic appearances of ischaemia in 21 of 28 (75%) patients and cardiac arrhythmias in three of 28 patients (10·7%). Arrhythmias were immediately associated with episodes of ischaemia in two; ischaemia preceding arrhythmia in one, and following sustained arrhythmia in one.

In conclusion, the incidence of arrhythmias during episodes of reversible cardiac ischaemia is low in patients with angina resulting from coronary artery disease. Treatment that prevents ischaemia might be expected to reduce the incidence of fatal cardiac arrhythmias in such patients. Arrhythmias that precipitate ischaemia are rare but are important to suppress when they arise.

Reciprocal ST depression in myocardial infarction: relation to exercise-induced ST depression

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In acute myocardial infarction, ST depression in leads distant from those showing ST elevation has been considered "reciprocal" but could reflect local ischaemia. To examine this possibility, we have reviewed 103 consecutive patients who underwent exercise testing soon after infarction. Treadmill exercise testing was performed a mean of 12 (five to 30) days after infarction using a modified Naughton procedure. Thirty-five (34%) of these patients had had "reciprocal" changes within 48 hours of infarction defined as ST depression ⩾1 mm at a distance from the infarct site. Twenty-one (61%) of the 35 had exercise-induced ST depression in the leads previously showing "reciprocal" change. Twelve of the remaining 14 subsequently had symptom limited exercise testing; two showed ST depression in the same site as the "reciprocal" change.

Thus, 66% of those with "reciprocal" change had ST depression on exercise in the same leads. Coronary anatomy was examined in eight of these by arteriography and in one at necropsy; all but one had a ⩾50% stenosis in a coronary artery supplying the "reciprocal" territory additional to disease in the vessel to the infarct site.

These findings suggest that "reciprocal" change may reflect ischaemia in territory distant from the infarction.

Orthotopic vs. heterotopic cardiac transplantation: haemodynamic and physiological factors

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Heart transplantation has been successfully carried out since 1960 based on the technical procedure described by Lower and Shumway. It was not until 1967, however, that the procedure was attempted in humans and the surgical technique has been essentially unchanged since. Shortly after the initiation of human cardiac transplantation episodes of acute post-operative right sided heart failure were noted in some patients in whom the preoperative pulmonary vascular resistance was substantially raised. It seemed that the new heart could not adapt rapidly enough to the high pressures necessary to the right heart and thus rapidly failed. Research into a solution to this catastrophic complication led to the development of the heterotopic transplant in which a new heart was "piggy-backed" onto a left ventricle allowing the native right ventricle to continue to supply the pulmonary circuit at its own chronically high pressure. Some investigators felt this to be a superior technique to orthotopic transplant as it allowed for possible recovery of the damaged native heart and resulted in eventual removal of the transplant in one case as the native's heart function improved. Heterotopic transplantation, however, is a more technically complex surgical procedure, leading to substantial alterations in flow characteristics and compliance between the two hearts. The potential benefit to the damaged native left ventricle is not guaranteed and there are significant risks of thrombus and embolus associated with the blood flow characteristics of the heterotopic procedure. A study was performed to outline the differences between the two procedures and shows a superior result with orthotopic. The two procedures were compared; echocardiographic features of the wall and valve motion were studied. Simultaneous phonocardiography, apexcardiography, and electrocardiography showed unique physiological features of the heterotopic transplant. Catheterisation studies corroborated these findings, and suggested progressive deterioration of a native heart in a heterotopic transplant because of disparate pressures and volumes. Thus it is shown that heterotopic transplant is not necessarily a superior technique and may in fact contribute to further deterioration of the native heart and necessitate further intervention.

Inverted circadian blood pressure rhythm in autonomic failure

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We have studied six subjects with autonomic failure (Shy-Drager or idiopathic type) using ambulatory intra-arterial pressure monitoring. All were monitored for at least 24 hours during which they were fully ambulant. Four were studied for an additional 24 hours during which they were restricted to bed. Tape recordings were computed to obtain mean hourly values of heart rate, and systolic and diastolic blood pressure from which circadian curves were derived.

Heart rate curves were normal in shape but the amplitude of the day-night change was reduced. The pattern of blood pressure change was, however, completely inverted from normal, with highest pressures occurring shortly after retiring for the night and then falling steadily to the nadir shortly after awakening, with a gradual rise thereafter. This pattern was highly consistent among the group and was generally unchanged during the period of bed rest. There was little effect of awakening on the underlying trend of blood pressure.

The low pressures in the early morning coincided with the exacerbation of orthostatic symptoms that many such patients report. Also, the night time pressures were often surprisingly in the hypertensive range. The pattern demonstrated appears to be highly relevant to clinical features of this condition and suggests potentially valuable approaches to treatment.

Changes in plasma potassium and the electrocardiogram induced by adrenaline and the effect of beta blockade on them

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We have previously reported on transient hypokalaemia in acute myocardial infarction. To investigate our hypothesis that this might be the result of increased circulating catecholamines, we have infused adrenaline in normal volunteers to the levels observed after myocardial infarcion.

Nine subjects were studied on three occasions after pretreatment with placebo, atenolol, or timolol. Adrenaline, 0·06 μg/kg per min, was infused over 90 minutes; plasma potassium was measured serially and a single lead electrocardiogram was recorded.

Pretreatment did not significantly alter plasma potassium (4·05, 4·03, and 4·09 mmol/l after placebo, atenolol and timolol, respectively). During infusion, plasma potassium fell to 3·21 mmol/l ($p<0{\cdot}001$) after placebo, and to 3·67 mmol/l after atenolol; it rose to 4·25 mmol/l after timolol.

Pretreatment did not alter the QTc interval. During infusion QTc rose from 0·36 to 0·4 s ($p<0·01$) after placebo and was unchanged after atenolol and timolol. During infusion after placebo, T wave amplitude decreased and two subjects developed U waves; the decrease in T wave amplitude was less after atenolol and absent after timolol.

Thus, increased plasma adrenaline may be a factor in the production of both hypokalaemia and arrhythmias after myocardial infarction and the prevention of hypokaleaemia and of abnormalities of repolarisation may contribute to the beneficial effects of beta blockade in this context.

Endogenous progesterone and blood pressure

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The amount of progestogen, as well as oestrogen, in oral contraceptives influences the risk of arterial disease in oral contraceptive users. The use of progestogens in hormone replacement regimens for menopausal symptoms is increasing, so there is added reason for assessing the effects of progestogens. The risk of ischaemic heart disease and stroke resulting from progestogens in oral contraceptive may be mediated through a rise in blood pressure. In the Northwick Park Heart Study, data from nearly 300 white women aged 44 years or less and not taking oral contraceptives show that blood pressure was significantly raised on those days of the menstrual cycle when progesterone levels would be expected to be highest. There was a systolic pressure difference of about 10 mmHg between the highest and lowest mean values for individual days of the cycle. Differences in age, indices of obesity, and smoking habit were not responsible for the differences in pressure. There was no correlation between pressure and anticipated levels of hormones other than progesterone. The hypothesis that serum progesterone levels might be correlated with level of blood pressure had not been formulated when the pressure measurements were made, so that finding is unlikely to be the result of bias.

Cardiomyopathy in Friedreich's ataxia

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Cardiomyopathy occurs commonly in Friedreich's ataxia and is often the cause of death. Some echocardiographic studies, but not all, have suggested that the cardiac pathology may be identical to hypertrophic obstructive cardiomyopathy. It has been speculated that catecholamine inbalance in Friedreich's ataxia may stimulate the cardiac muscle abnormality. We elected to compare the M-mode echocardiograms of patients with Friedreich's ataxia with those of patients who had similar hereditary spinal degeneration syndromes. Analysis of echocardiograms was made by two observers without prior knowledge of the neurological disorder.

Thirty-three children aged 4 to 18 years were studied. Ten of 11 with classical Friedreich's ataxia and two of three with atypical ataxia had abnormal echocardiograms. None of the other 21 patients with neurological disorders had echocardiographic abnormalities. The abnormal echocardiograms all showed increased thickness of the ventricular septum and left ventricular posterior wall. Asymmetric septal hypertrophy and systolic anterior motion of the mitral valve were present in three patients. Early systolic closure of the aortic valve occurred in one.

This study has shown that cardiac involvement is almost invariable in Friedreich's ataxia but does not occur in other similar neurological disorders. The cardiomyopathy appears to be heterogeneous. Echocardiography is a sensitive method of diagnosis and may help differentiate Freidreich's ataxia from other disorders.

Changes in left ventricular mass, volume, and function after surgery for chronic aortic regurgitation

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In order to assess the reversibility of the myocardial adaptations and dysfunction accompanying chronic aortic regurgitation, we studied serial changes in left ventricular mass and volume in 67 patients with this chronic volume overload who survived aortic valve replacement. There changes were correlated with postoperative clinical, haemodynamic, and histological data. Patients were divided into two groups: those in whom the left ventricular echocardiographic diameters returned to normal after operation (group A), and those with postoperative dilatation (group B). The postoperative end-diastolic diameter returned to normal in 51 patients (group A); a parallel reduction of left ventricular voltages and echocardiographic estimates of ventricular mass was noted in 86% of these cases. Out of the 16 patients with postoperative ventricular dilatation (group B), 14 had satisfactory valve function. After valve replacement, patients in this group B had persistent or progressive electrocardiographic abnormalities, unchanged estimates of ventricular muscle mass, altered segmental wall motion, and impaired haemodynamic responses to exercise.

Left ventricular biopsies were obtained before and one year after operation from four patients in group A and from eight patients in group B. Mean postoperative muscle fibre diameter had regressed significantly to 23·4μ in cases from group A, but remained massively increased (mean 32·5μ) in patients from group B. Increased interstitial collagen, degenerative ultrastructural changes, and reduced levels of myofibril-associated ATPase in pre- and postoperative biopsies correlated with impaired ventricular function and persistent dilatation and hypertrophy after surgery.

Preoperative echocardiographic and angiographic data could define the type and degree of ventricular dysfunction which was irreversible. The histological alterations seen in pre- and postoperative biopsies from those patients who experienced no functional improvement suggest that irreversible morphological changes contribute to a depressed cardiac function after surgery.

Relation between alcohol intake, myocardial dysfunction, and myocardial tissue enzyme activities

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The quantity of alcohol responsible for heart muscle disease in man is unknown.

Thirty patients with suspected cardiomyopathy were studied by catheterisation and myocardial biopsy. Detailed drinking histories were taken by an independent observer. Myocardial tissue enzyme activities were measured. This study compared the results of these three independent investigations.

Analysis of the drinking histories showed a clear division into two groups. Eleven patients (36%) consumed more than 80 g alcohol daily for 10 years and 15 patients (50%) consumed less than 40 g alcohol daily for 10 years. Only four patients (14%) consumed 40 to 80 g daily. Sixteen patients (52%) consumed in excess of 500 kg total lifetime intake of alcohol.

Myocardial enzyme activities have previously been shown to separate alcoholic heart muscle disease and dilated cardiomyopathy. In this study creatinine kinase activity correlated with daily alcohol consumption (40 g $p<0·02$, 80 g $p<0·005$) and total cumulative alcohol intake ($p<0·05$). Furthermore, alpha hydroxybutyric dehydrogenase:lactate dehydrogenase ratio correlated with left ventricular ejection fraction ($p<0·05$).

In conclusion, drinking in excess of 80 g alcohol daily for 10 years or cumulative lifetime intake greater than 500 kg is likely to result in alcoholic heart muscle disease. Myocardial damage reflected in abnormal enzyme activity may be seen in patients consuming 40 to 80 g alcohol daily.

Effect of intravenous amrinone on resting haemodynamic function in patients with congestive cardiac failure

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Department of Cardiology, St Thomas's Hospital, London

The effect of intravenous amrinone on resting haemodynamic function was investigated in 15 patients with congestive cardiac failure. 3·5 mg/kg amrinone produce appreciable and significant changes in cardiac index (+102%), ejection fraction (+36%), systemic vascular resistance (−57%), mean arterial pressure (−20 mmHg), and left ventricular end-diastolic pressure (−9·6 mmHg). 1·5 mg/kg amronone produced similar but smaller changes ($p<0·01$). These alterations were accompanied by only small increases in heart rate ($p<0·01$) and a small reduction in left ventricular end-diastolic volume ($p<0·02$). No change in max dP/dt, min dP/dt, $\left(\frac{\text{max dP/dt}}{\text{P}}\right)$, max $\left(\frac{\text{dP/dt}}{\text{P}}\right)$, KVmax, or the ratio of left ventricular end-systolic pressure to left ventricular end-systolic volume occurred. It is concluded that the beneficial effects of intravenous amrinone on the resting haemodynamics in our patients were attributable to vasodilatation, with the drug having no demonstrable inotropic effect.

Interaction between inotropism and vasodilatation in heart failure

J Bayliss, M Norell, R Canepa-Anson, S Reuben, P A Poole-Wilson, G C Sutton
Hillingdon Hospital, Uxbridge, Middlesex, and Cardiothoracic Institute, London

Although drugs used in heart failure may have inotropic or vasodilator properties, their clinical effects in patients may be similar. Furthermore, a combination of drugs with different pharmacological actions may be used to advantage. To examine these possibilities, we compared a non-glycosidic non-adrenergic inotropic agent (amrinone) and a betaagonist (pirbuterol), with a venodilator (isosorbide dinitrate) added to each drug.

After control measurements, oral amrinone (100 mg) or pirbuterol (20 mg) were given in random order to each of 13 patients, on successive days with isosorbide dinitrate (20 mg) given orally after two and a half hours. Control values were not significantly different before amrinone or pirbuterol were given. Significant ($p<0·01$) increases in cardiac index (65% with amrinone, 55% with pirbuterol) and falls in wedge pressure (27%, 19%), right atrial pressure (16%, 21%), and systemic vascular resistance (33%, 32%) occurred. Heart rate and blood pressure remained unchanged. The magnitude of the changes caused by amrinone and pirbuterol were not significantly different. The addition of isosorbide dinitrate caused further ($p<0·01$) falls in wedge and right atrial pressures, and a fall ($p<0·05$) in heart rate with each drug. Other variables remained unchanged.

Although amrinone and pirbuterol have different pharmacological properties, their acute haemodynamic effects in patients with chronic heart failure are indistinguishable. Both drugs produce an increase in cardiac output at lower filling pressure and systemic vasodilatation; the submaximal venodilatation may be enhanced by nitrates.

Immunosuppressive therapy in acute inflammatory myocarditis

K Daly, P J Richardson, E G J Olsen, J Pattison, G Jackson, D E Jewitt
King's College Hospital, Denmark Hill, London

This study describes the diagnosis of acute myocarditis and its treatment with immunosuppressive therapy. Twelve patients with a recent history of an infectious illness presented with acute dyspnoea and evidence of biventricular heart failure. Cardiac catheterisation and left ventricular biopsies were performed in all patients. Left ventricular angiography and echocardiography were compatible with dilated cardiomyopathy. Histology showed evidence of acute inflammatory myocarditis in nine patients. Serology suggested a viral aetiology in six patients (Coxsackie B in five, *Herpes simplex* in one), of whom two had negative biopsies. Seven patients were started on prednisone and azathioprine. Two patients received prednisone alone.

After two months treatment nine patients were restudied and eight showed symptomatic and haemodynamic improvement with a fall in left ventricular end-diastolic pressure from 26·4 to 15·2 mmHg, pulmonary artery systolic pressure from 40 to 27 mmHg, and a rise in ejection fraction from 26·8 to 49% and in cardiac index from 2·7 to 3·9 l/min per m. Histology in seven patients showed healing myocarditis. Two patients showed persisting acute myocarditis (one not treated, one on steroids alone).

Serology and myocardial histology are complementary in the diagnosis and management of this condition. The results of treatment suggest a role for combined immunosuppressive therapy.

Early and late results of surgical repair of lesions associated with corrected transposition

Jennie Metcalffe, Jane Somerville
Paediatric and Adolescent Unit, National Heart Hospital, London

Nineteen patients, 15 male and four female, aged 13 months to 47 years (mean 16 years) underwent surgical repair of lesions associated with corrected transposition. Ventricular septal defects were closed in 16 (multiple in two) and 11 had pulmonary stenosis. Seven of the 19 patients had important left atrioventricular valve regurgitation, five requiring surgical correction. Conduction disturbances or arrhythmias were present preoperatively in eight: congenital complete heart block or complete atrioventricular dissociation (five), established or intermittent atrial fibrillation (three). Four patients had previous surgery: banding of the pulmonary artery (one) and systemic-pulmonary shunt (three). Seven perioperative deaths occurred, six resulting from low output state: failure to close multiple ventricular septal defects (one), new and precipitous onset of complete heart block (two), poor systemic ventricular function (one), and progressive haemodynamic deterioration (two). One death followed septic meningitis complicating temporary transvenous pacing. Perioperative onset of complete heart block occurred in five requiring permanent pacing.

Twelve survivors were followed for three to eight years with postoperative cardiac catheterisation in 10 at one to 36 months in addition to assessment with M-mode and two dimensional echocardiography, ambulatory monitoring, and exercise testing. Left atrioventricular valve regurgitation was present in 10, with subsequent valve replacement in one. Four late deaths occurred at 15 months to four years resulting from indirect complications of permanent pacing (two), complex arrhythmias (one), and non-cardiac cause (one). Of the eight current survivors, four have severe residual left atrioventricular valve regurgitation (two with pacemakers), and only two are completely asymptomatic.

The presence of conduction system abnormalities and the function of the left atrioventricular valve and morphological right ventricle influence not only the natural history of patients, but also the unnatural history of patients after surgical treatment of associated lesions in corrected transposition. The results of this series suggest that direct repair is indicated only in the severely symptomatic patients.

Complications of long-term prostaglandin E_2 therapy in infants with complex heart disease

P Morrell, G R Sutherland, H H Bain, S Hunter
Freeman Hospital, Newcastle Upon Tyne

The short term use of prostaglandin E_2 to maintain duct patency is well established in the treatment of duct dependent congenital heart disease. Few reports, however, exist of the effectiveness and complication rate of long-term PGE_2 therapy.

Over the past three years, 31 such infants (average gestation 39 weeks, birth weight 3·0 kg) were started on oral prostaglandin E_2 therapy. Nineteen infants were treated for a period of less than seven days before palliative surgery. Apart from transient pyrexia these infants had no serious side effects. A further 12 infants were maintained on oral prostaglandin E_2 long term (mean 28·5 days, nine with pulmonary atresia, two tricuspid atresia, one critical pulmonary stenosis). All developed side-effects attributable to oral prostaglandin E_2 therapy. Six infants had severe apnoeic episodes requiring resuscitation. Ten infants had recurrent pyrexias. Eight had intermittent diarrhoea (three with melaena). A further three infants developed a persistent severe metabolic acidosis (average duration of therapy 47 days) for which no other cause could be determined. All died as a result of this.

We conclude that short term prostaglandin E_2 administration is both effective and safe. In our experience, however, its long-term use in infants with congenital heart disease is more hazardous than previously reported. The incidence and mechanism of the late spontaneous metabolic acidosis require further elucidation.

Role of suprasternal two dimensional echocardiography in assessment of neonate and infant with congenital heart disease

J F Smallhorn, J Huhtra, R H Anderson, F J Macartney
The Hospital for Sick Children, Great Ormond Street, London

Though two dimensional echocardiography has made a major impact on the assessment of the sick neonate and infant, the main emphasis has been on intracardiac anatomy demonstrated by subcostal and praecordial cuts rather than direct visualisation of supracardiac structures. The aims of the study were to evaluate the ability of suprasternal echocardiography to demonstrate normal anatomy and to determine which anomalies could be visualised from this approach. Studies were made on a total of 193 cases. In 50 cases with normal supracardiac anatomy reliable delineation was possible in all cases. In particular, the side of the aortic arch, brachiocephalic branching, and continuity of the pulmonary arteries could be shown. Specific patterns were present for the majority of cases with supracardiac abnormalities. In the group, 15 cases had total anomalous pulmonary venous drainage, four aorticopulmonary window, 13 truncus arteriosus, 30 coarctation of the aorta, 15 pulmonary atresia, 50 persistent ductus arteriosus, 10 left superior vena cava to coronary sinus, two anomalous origin of left pulmonary artery from the aorta, and four interrupted aortic arch.

Thus two dimensional echocardiography allows a reliable assessment of the normal supracardiac anatomy and enables the examiner to obtain detailed information about defects not available from the praecordial and subcostal windows.

Demonstration of defects of interventricular septum in adults by two dimensional echocardiography

K Evemy, G Sutherland, S Hunter
Freeman Hospital, Newcastle Upon Tyne

The ability of two dimensional echocardiography to identify and classify ventricular septal defects in adults was studied prospectively in 56 patients (age range 15 to 78 years). Included were 41 patients with congenital heart disease (24 with isolated septal defects) and 15 patients with post-infaction defects. A multiplane scanning technique of examination was routinely recorded. Defects were considered identified only when consistently visualised in two echocardiographic planes. The echocardiographic findings were subsequently correlated with clinical, catheterisation, surgical, and postmortem information.

Twenty-one congenital defects were identified and correctly classified. Defects associated with complex lesions or isolated Eisenmenger defects were reliably identified, as were isolated defects with Qp:Qs>2:1. All 11 isolated defects not identified appeared clinically small and in eight catheterisation demonstrated a Qp:Qs>1·6:1.

Post-infarction defects in the trabecular septum were identified in 13 patients, with the defect visualised in 10. In the remaining three patients contrast echocardiography demonstrated right to left ventricular shunting.

We conclude that two dimensional echocardiography is extremely effective in identifying and predicting the haemodynamic significance of adult congenital ventricular septal defects. In addition, this study emphasises the value of two dimensional echocardiography in demonstrating post-infarction defects, either by direct visualisation or by the use of contrast echocardiography.

Notices

The Fifth Symposium on Echocardiology will be held at the Erasmus University, Rotterdam, the Netherlands, 22 to 25 June 1983. For further details, please write to Mr H Rijsterborgh, Erasmus University, Ee 2302a, PO Box 1738, 3000 DR Rotterdam, the Netherlands.

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

British Cardiac Society

The Autumn Meeting will take place at Wembley on 6 and 7 December 1982 and the closing date for receipt of abstracts is 11 August 1982.

The Annual General Meeting for 1983 will take place in Bristol on 12 and 13 April, and the closing date for abstracts will be 4 January 1983.

The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts will be 28 July 1983.

International conference on cardiac arrest and resuscitation

This conference, sponsored by the British Heart Foundation in association with the Community Resuscitation Advisory Council, BASICS, and the Royal Postgraduate Medical School, Hammersmith, will be held in Brighton on 19 to 21 October 1982. Inquiries to: Conference Services Limited, 3 Bute Street, London SW7 3EY.

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Original Articles:

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Eulo Lupi-Herrera, Julio Sandoval,
Mario Seoane, and David Bialostozky
EDITORIAL:Unexplained Pulmonary Hypertension
Alfred P. Fishman
The Effects of Intravenous Verapamil on Hemodynamic Status of Patients with Coronary Artery Disease Receiving Propanolol
Joshua Kieval, Edward B. Kirsten,
Kenneth M. Kessler, Stephen M. Mallon,
and Robert J. Myerburg
Hemodynamic Consequences of Combined Beta-adrenergic and Slow Calcium Channel Blockade in Man
Milton Packer, Jose Meller, Norma Medina,
Madeline Yushak, Harry Smith,
James Holt, Juan Guerrero,
G. Daniel Todd,
Russell G. McAllister, Jr., and
Richard Gorlin
EDITORIAL: Calcium-entry Blockade, Beta-adrenergic Blockade and the Reflex Control of Circulation
Stephen N. Oesterle and John S. Schroeder
Alterations in Left Ventricular Function and Coronary Hemodynamics with Captopril, Hydralazine and Prazosin in Chronic Ischemic heart Failure: A Comparative Study
Jean-Lucien Rouleau, Kanu Chatterjee,
William Benge, William W. Parmley, and
Beverley Hiramatsu
Attenuation of Exercise Conditioning by Beta-adrenergic Blockade
David L. Sable, H.L. Brammell,
Mark W. Sheehan, Alan S. Nies,
John Gerber, and Lawrence D. Horwitz
Reversal of Exercise-induced Hemodynamic and Electrocardiographic Abnormalities After Coronary Artery Bypass Surgery
Radha J. Sarma and Miguel E. Sanmarco
Analysis of Left Ventricular Pressure During Isovolumic Relaxation in Coronary Artery Disease
D.S. Thompson, C.B. Waldron, S.M. Juul,
N. Naqvi, R.H. Swanton, D.J. Coltart,
B.S. Jenkins, and M.M. Webb-Peploe
Effect of Large Variations in Preload on Left Ventricular Peformance Characteristics in Normal Subjects
J.V. Nixon, R. Gordon-Murray,
Peter D. Leonard, Jere H. Mitchell, and
C. Gunnar Blomqvist
Effect of Hydralazine on Aortic Rupture Induced by B-Aminopropionitrile in Turkeys
Charles F. Simpson and W. Jape Taylor
Patterns of Progression of Aortic Stenosis: A Longitudinal Hemodynamic Study
Stephen Wagner and Arthur Selzer
Size and Motion of the Mitral Valve Annulus in Man. II. Abnormalities in Mitral Valve Prolapse
John A. Ormiston, Pravin M. Shah,
Chuwa Tei, and Maylene Wong
Echocardiographic Detection of Left Main Coronary Artery Obstruction
Lawrence D. Rink, Harvey Feigenbaum,
Robert W. Godley, Arthur E. Weyman,
James C. Dillon, John F. Phillips, and
Jane E. Marshall
Radionuclide Measurement of Left Ventricular Volume: Comparison of Geometric and Counts-based Methods
Barry M. Massie, Barry L. Kramer,
Edward W. Gertz, and
Steven G. Henderson
Effect of Flow-independent Reduction of Metabolism on Regional Myocardial Clearance of ^{11}C-Palmitate
Rene A. Lerch, Steven R. Bergmann,
Hans D. Ambos, Michael J. Welch,
Michel M. Ter-Pogossian, and
Burton E. Sobel
Contrast Enhancement of Myocardial Infarction: Dependence on Necrosis and Residual Blood Flow and Relationship to Distribution of Scintigraphic Imaging Agents
Charles B. Higgins, Phillip L. Hagen,
John D. Newell, Walter S. Schmidt, and
Frank H. Haigler
Characterization of Nontransmural Myocardial Infarction by Positron-emission Tomography
Edward M. Geltman, Daniel Biello,
Michael J. Welch,
Michel M. Ter-Pogossian,
Robert Roberts, and Burton E. Sobel
Estimation of Acute Myocardial Infarct Size in Man by serum CK-MB Measurements
Peer Grande, Birgit Fischer Hansen,
Claus Christiansen, and Jørgen Naestoft
Intravenous Hyaluronidase Therapy for Myocardial Infarction in Man: Double-blind Trial to Assess Infarct Size Limitation
John A. Cairns, Douglas A. Holder,
Paul Tanser, and Eleftheria Missirlis
Intravenous Isosorbide Dinitrate in Patients with Refractory Pump Failure and Acute Myocardial Infarction
Babeth Rabinowitz, Israel Tamari,
Ella Elazar, and Henry N. Neufeld
Pathophysiology of Chest Pain in Patients with Cardiomyopathies and Normal Coronary Arteries
André Pasternac, Jacques Noble,
Yves Streulens, Robert Elie,
Claudia Henschke, and
Martial G. Bourassa
Factors in Predicting Blood Pressure Change
David Sparrow, Arthur J. Garvey,
Bernard Rosner, and
H. Emerson Thomas Jr.
A Comparative Study of Serum Lipids Between Belgium and Korea
H. Kestellot, C.S. Lee, H.M. Park,
C. Kegels, J. Geboers, J.H. Claes, and
J.V. Joossens
Termination of Ventricular Tachycardia with Ventricular Stimulation: Salutary Effect of Increased Current Strength
Harvey L. Waxman, Michael E. Cain,
Allan M. Greenspan, and
Mark E. Josephson

Case Reports:

Pulmonary Atresia with Intact Ventricular Septum and Ventriculocoronary Communications: Surgical Significance
William N. O'Connor, Carol M. Cottrill,
Gregory L. Johnson,
Jacqueline A. Noonan, and
Edward P. Todd
Bilateral Coronary Artery-Pulmonary Artery Fistulas. Report of Five Cases and Review of the Literature
Donald S. Baim, Howard Kline, and
James F. Silverman
Detection of Mitral Ring Abscess by Two-dimensional Echocardiography
Kenji Nakamura, Shin Suzuki,
Gengi Satomi, Hisae Hayashi, and
Koshichiro Hirosawa
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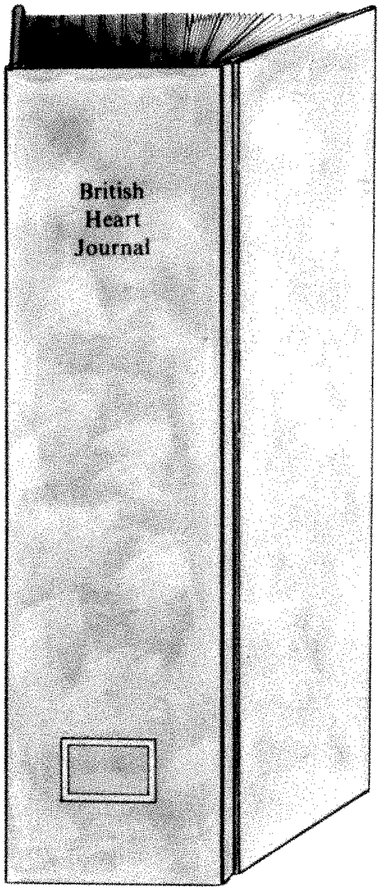

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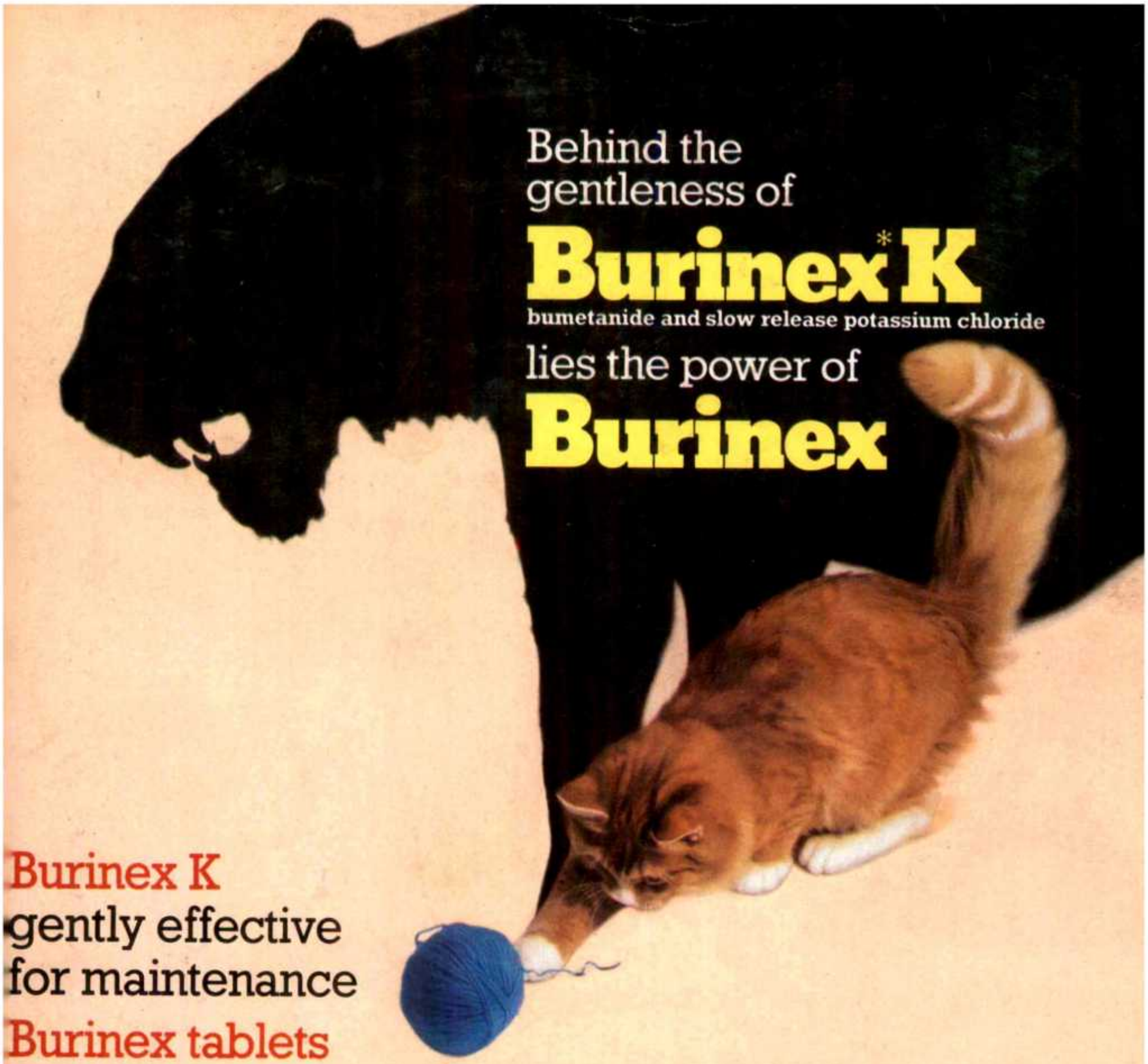

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Two dimensional echocardiographic diagnosis of situs *J C Huhta, J F Smallhorn, F J Macartney* 97

Isolated anterior mitral cleft. Two dimensional echocardiographic assessment and differentiation from "clefts" associated with atrioventricular septal defect *J F Smallhorn, M de Leval, J Stark, J Somerville, J F N Taylor, R H Anderson, F J Macartney* 109

Mitral valve replacement in children. Comparative study of pre- and postoperative haemodynamics and left ventricular function *E G Benmimoun, B Friedli, W Rutishauser, B Faidutti* 117

Independence of changes in left ventricular diastolic properties of pericardial pressure *P J Oldershaw, E Shapiro, M Mattheos, M G St John Sutton, D Gibson* 125

Exercise testing in mitral valve prolapse before and after beta blockade *E G Abinader, J Shahar* 130

Effect of heparin on plasma free fatty acid concentrations after acute myocardial infarction *R A Riemersma, R Logan, D C Russell, H J Smith, J Simpson, M F Oliver* 134

Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man *K J Hellestrand, R S Bexton, A W Nathan, R A J Spurrell, A J Camm* 140

Role of the Frank-Starling mechanism during maximal semisupine exercise after oral atenolol *K Andersen, H Vik-Mo* 149

Diurnal variation in exercise responses in angina pectoris *M Joy, C M Pollard, T O Nunan* 156

Influence of R wave analysis upon diagnostic accuracy of exercise testing in women *C Ilsley, R Canepa-Anson, C Westgate, S Webb, A Rickards, P Poole-Wilson* 161

Computerised cardiological case notes *K N Williams, I A B Brooksby, J Morrice, S Houseago, M M Webb-Peploe* 169

Case reports
- Large calcified right atrial myxoma in a newborn. Rare cause of neonatal death *S B Dianzumba, G Char* 177
- Unusual vascular ring in infant with pulmonary atresia and ventricular septal defect *R McKay, J Stark, M de Leval* 180
- Permanent right bundle-branch block heralded by intermittent block and ventricular extrasystoles. A 13-year observation *Y Watanabe, H Kishi* 184
- Severe subpulmonary obstruction caused by an aneurysmal tissue tag complicating an infundibular perimembranous ventricular septal defect *M Bonvicini, G Piovaccari, F M Picchio* 189

Notices 192

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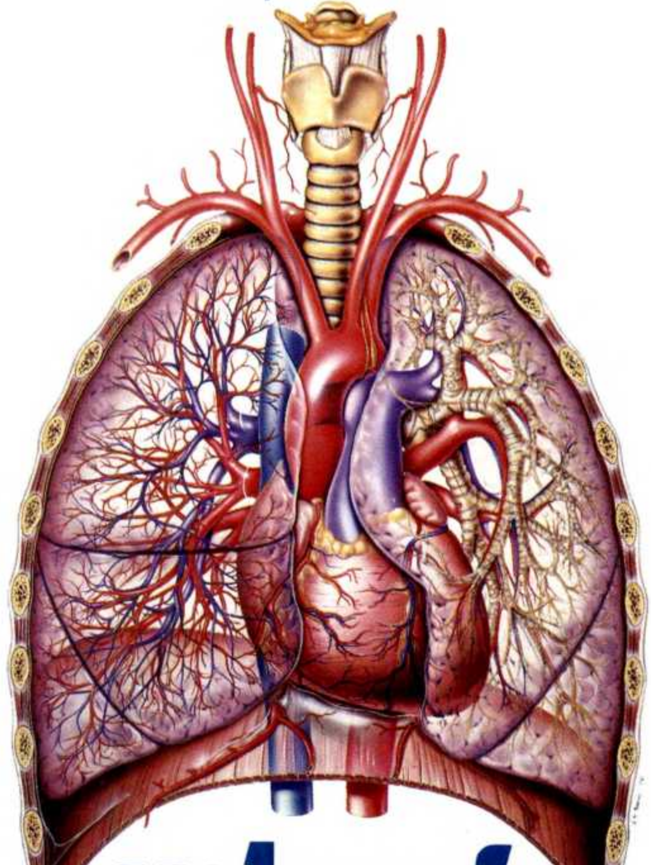

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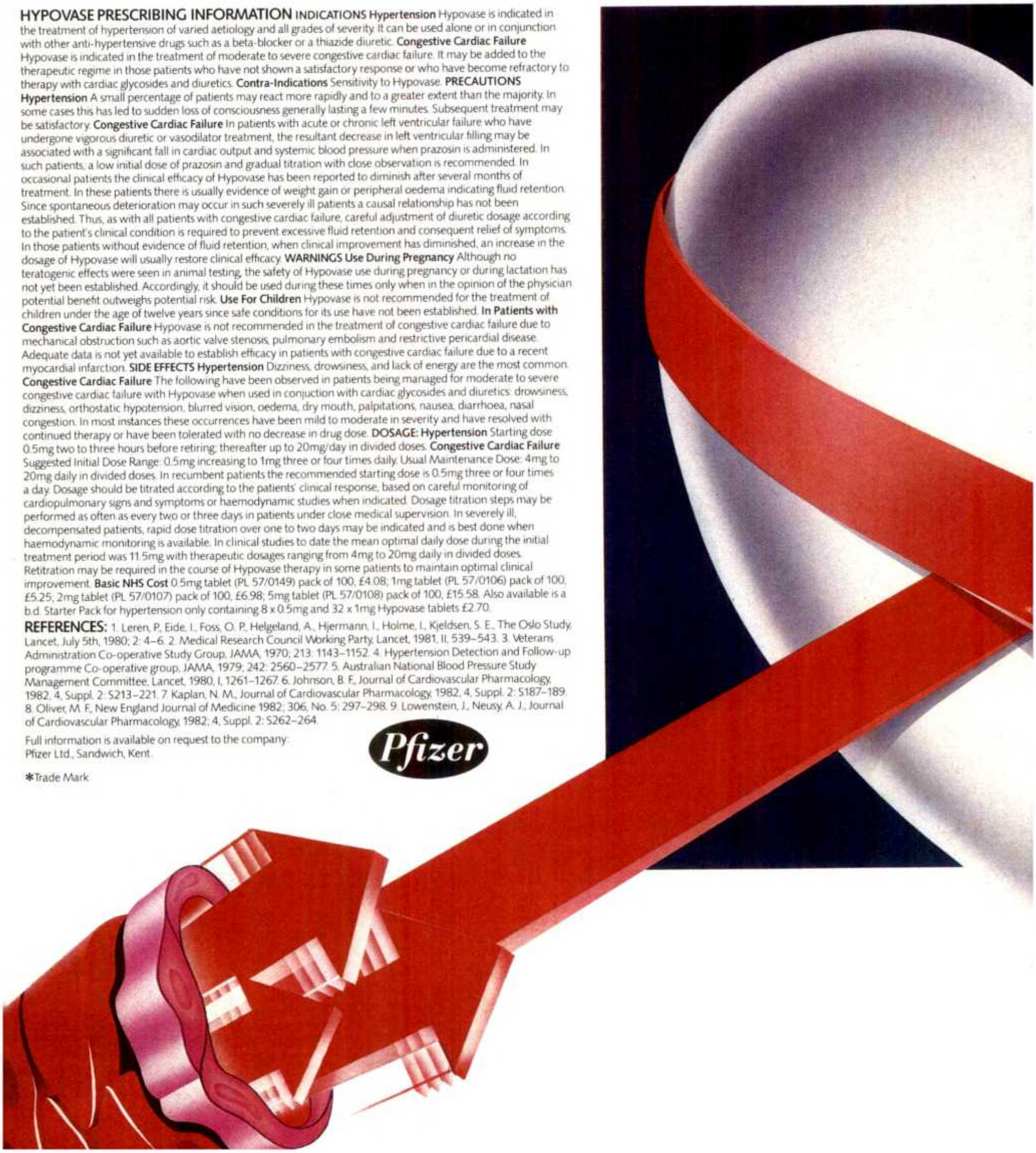

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REFERENCES: 1. Leren, P., Eide, I., Foss, O. P., Helgeland, A., Hjermann, I., Holme, I., Kjeldsen, S. E., The Oslo Study, Lancet, July 5th, 1980; 2: 4–6. 2. Medical Research Council Working Party, Lancet, 1981, II, 539–543. 3. Veterans Administration Co-operative Study Group, JAMA, 1970; 213: 1143–1152. 4. Hypertension Detection and Follow-up programme Co-operative group, JAMA, 1979; 242: 2560–2577. 5. Australian National Blood Pressure Study Management Committee, Lancet, 1980, I, 1261–1267. 6. Johnson, B. F., Journal of Cardiovascular Pharmacology, 1982, 4, Suppl. 2: S213–221. 7. Kaplan, N. M., Journal of Cardiovascular Pharmacology, 1982, 4, Suppl. 2: S187–189. 8. Oliver, M. F., New England Journal of Medicine 1982; 306, No. 5: 297–298. 9. Lowenstein, J., Neusy, A. J., Journal of Cardiovascular Pharmacology, 1982; 4, Suppl. 2: S262–264.

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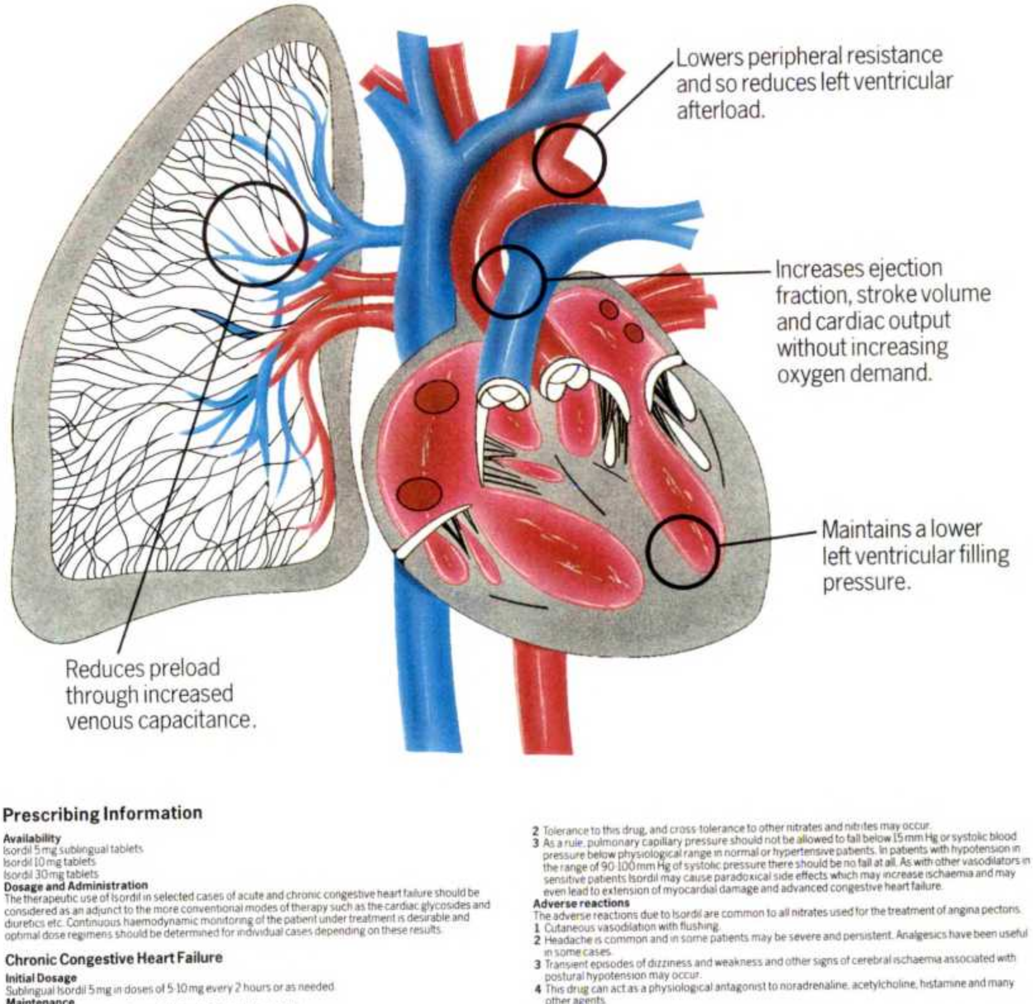

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Br Heart J 1982; 48: 97–108

Two dimensional echocardiographic diagnosis of situs

JAMES C HUHTA,* JEFFREY F SMALLHORN, FERGUS J MACARTNEY

From The Hospital for Sick Children, Great Ormond Street, London

SUMMARY At present there is no reliable method of recognising atrial isomerism by two dimensional echocardiography. We therefore used two dimensional echocardiography to examine 158 patients including 25 with atrial isomerism and four with situs inversus. Particular attention was paid to the short and long axis subcostal scans of the abdomen.

Using the position of the inferior vena cava and the aorta with respect to the spine it was possible to separate those with situs solitus from the others. Two false positives for abnormal situs had exomphalos. In situs solitus the aorta lay to the left of the spine and the inferior vena cava lay to the right. One patient with situs solitus and azygos continuation of the inferior vena cava also had inferior vena cava to right atrial connection. In the four patients with situs inversus the mirror image of the normal pattern was present.

In nine patients with right isomerism the inferior vena cava and aorta ran together on one or other side of the spine. The inferior vena cava, anterior to the aorta at the level of the diaphragm, received at least the right hepatic veins (normal or partial anomalous hepatic venous connection).

Of the 16 patients with left isomerism, 14 had azygos continuation of the inferior vena cava which was visualised posterior to the aorta in all but two. All patients with left isomerism had total anomalous hepatic venous connection to one or both atria via one or two separate veins.

Two dimensional echocardiography therefore provides the means of detecting abnormal atrial situs and of diagnosing right or left isomerism in the great majority of patients, if not all.

Accurate determination of atrial situs is the foundation of a segmental approach to the diagnosis of congenital malformations and malpositions.[1-4] Many clinical clues are available for the recognition of patients with abnormal situs, and the importance of identifying left and right isomerism has been emphasised by many authors.[5-8] A non-invasive examination such as two dimensional echocardiography which could be used routinely to determine situs would be very useful. At present, the determination of atrioventricular connection by two dimensional echocardiography is speculative and other techniques are necessary to assign atrial situs.[8-10] Alerted to the presence of abnormal situs, the echocardiographer will pay particular attention to the systemic and pulmonary venous connections.

To investigate the diagnosis of situs by two dimensional echocardiography we examined 158 consecutive patients including 11 who were known to have abnormal situs. Over this five month period 18 additional patients were diagnosed prospectively as having abnormal situs and were correctly categorised into those with situs inversus, right isomerism, or left isomerism.

The purpose of this study was to consider criteria for the two dimensional echocardiographic assessment of situs. Two questions were considered.

(1) Can two dimensional echocardiography be used accurately to separate patients with abnormal situs from those with situs solitus?

and, if so,

(2) Can those criteria be used further to subdivide the abnormal situs patients into those with situs inversus, right isomerism, and left isomerism?

Subjects and methods

Between September 1981 and January 1982, 158 consecutive patients had a two dimensional echocardiographic examination at The Hospital for Sick Children, Great Ormond Street, by one of us (JCH or JFS). The ages of the patients ranged from 1 day to 16

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years, with a mean age of 2·9 years. Forty-three per cent were under 1 year of age. A complete examination was performed in each patient, including subcostal, parasternal, apical, and suprasternal views.[11] Sequential analysis of the anatomy was performed using the terms and definitions suggested by Tynan *et al.*[12] Particular attention was paid to the short and long axis subcostal scans of the abdomen and the systemic venous return. In order to recognise absence of the inferior vena cava immediately inferior to the cardiac atria it was important to recognise positively the crus of the diaphragm, which could superficially resemble a venous structure. During this time, 11 patients previously diagnosed as having abnormal situs were recalled and also examined by two dimensional echocardiography in the same way without knowledge of the type of situs abnormality.

Patients excluded were those without confirmation of situs by either filtered beam high kilovoltage chest x-ray,[10] surgery, or necropsy.[13]

Eight patients had necropsy confirmation of situs including three with left isomerism, and 39 patients had open heart surgery.

Results

DIAGNOSIS OF SITUS BY TWO DIMENSIONAL ECHOCARDIOGRAPHY

There was a typical appearance of the two dimensional echocardiographic short axis subcostal view of the abdomen in the patients with situs solitus (Fig. 1). At approximately the level of T10, the aorta lay to the left of the spine, being recognisable by its typical systemic arterial pulsation. The inferior vena cava was located opposite to the aorta on the right of the spine and was further identified by long axis subcostal views showing the right hepatic venous connection and inferior vena cava to the right atrial junction.

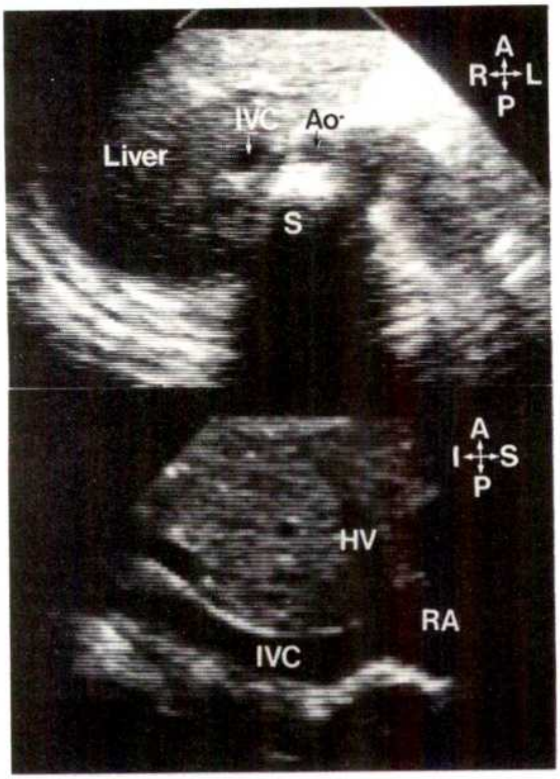


Fig. 1 *Two dimensional echocardiographic appearance of situs solitus. In the short axis subcostal view (upper panel) the aorta (Ao) and inferior vena cava (IVC) are symmetrical with respect to the spine (S) with the aorta to the left (L) and the liver lateralised to the right (R). In the long axis (lower panel) the inferior vena cava receives the hepatic veins (HV) and connects to the right atrium (RA). A, anterior; I, inferior; P, posterior; S, superior.*

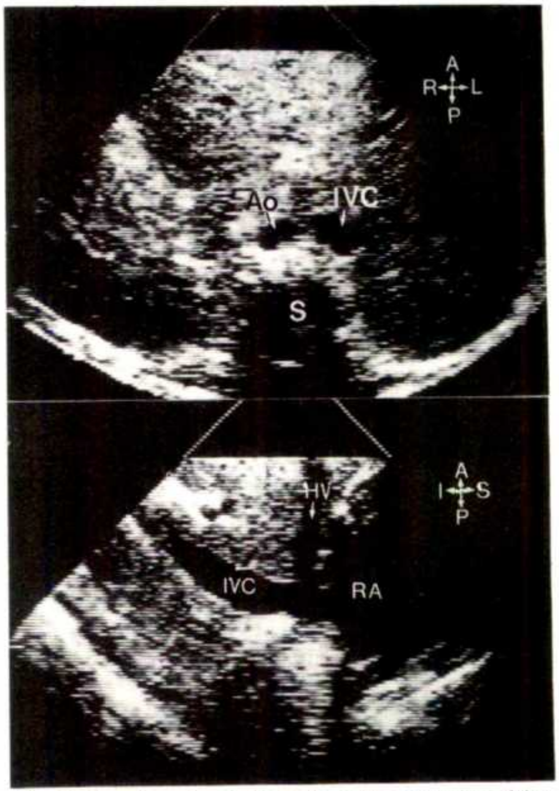


Fig. 2 *Two dimensional echocardiographic appearance of situs inversus. A mirror image of the situs solitus pattern is present in the short axis view (upper panel) with the aorta (Ao) on the right (R). The left sided inferior vena cava (IVC) receives hepatic veins (HV) and connects to the morphological right atrium (RA). (Abbreviations as in Fig. 1.)*

Table 1 *Inferior vena cava/aorta position*

	Inferior vena cava/aorta symmetry	*Inferior vena cava/aorta run together*	*Other*	*Totals*
Inversus	4	0	0	4
Right isomerism	0	9	0	9
Left isomerism	0	1	15	16

Patients with situs inversus were found to have a mirror image of the situs solitus pattern (Fig. 2), with the aorta to the right and the inferior vena cava to the left, both vessels again being symmetrically disposed with respect to the spine (Table 1). The hepatic venous connections and the inferior vena caval to right atrial junction also formed the mirror image of situs solitus with the hepatic veins connecting to the inferior vena cava or joining the atrium with the inferior vena cava.

Right or left isomerism could be diagnosed by the abnormal position of the inferior vena cava and aorta in the abdomen. These two entities could then be distinguished by the type of positional abnormality combined with the pattern of hepatic venous and inferior vena cava to right atrial connection.

In right isomerism, the aorta and inferior vena cava ran together at the subcostal level, with the aorta posterior, either to the right or left of the spine (Fig. 3 upper panels). The right hepatic vein connected to the inferior vena cava and could be visualised on the same side of the spine (Fig. 3 lower panels), (Table 1).

In left isomerism, the aorta was usually midline (13 patients), though it was to the right in two and to the left in one. No normal inferior vena cava was seen on this level. Instead azygos continuation of the inferior vena cava posterior to the aorta, either to the left or right of the spine, was present in 14 patients (Table 1; Fig. 4 upper panels). In two of these patients the azygos vein was not visualised and only the midline aorta could be seen. In the two remaining patients the suprarenal inferior vena cava connected to the inferior aspect of the atrium (left sided in one and right sided in one).

The crus of the diaphragm appeared as an echo free line close to the anticipated position of the normal inferior vena cava immediately below the cardiac

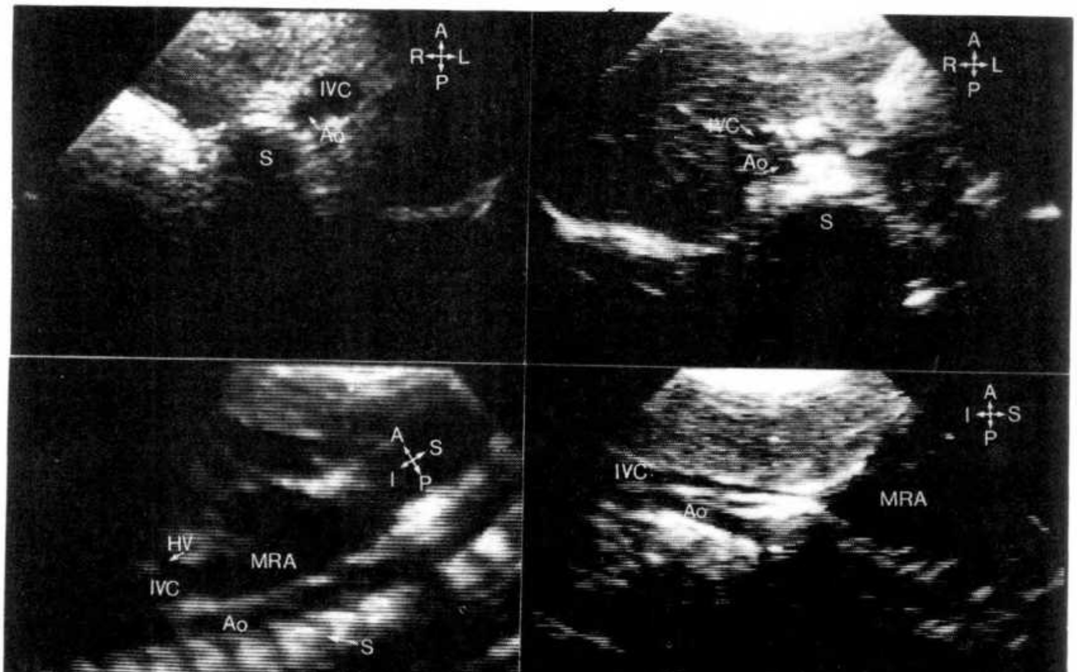


Fig. 3 *Two dimensional echocardiographic appearance of right isomerism. The aorta (Ao) and inferior vena cava (IVC) run together with the inferior vena cava anterior and lateral either to the left (L) (left upper panel) or to the right (R) (right upper panel). The inferior vena cava receives hepatic venous connection (HV) and connects to the inferior aspect of the morphological right atrium (MRA) (lower panels). Note that the inferior vena cava and aorta may be visualised in the same scan. (Abbreviations as in Fig. 1.)*

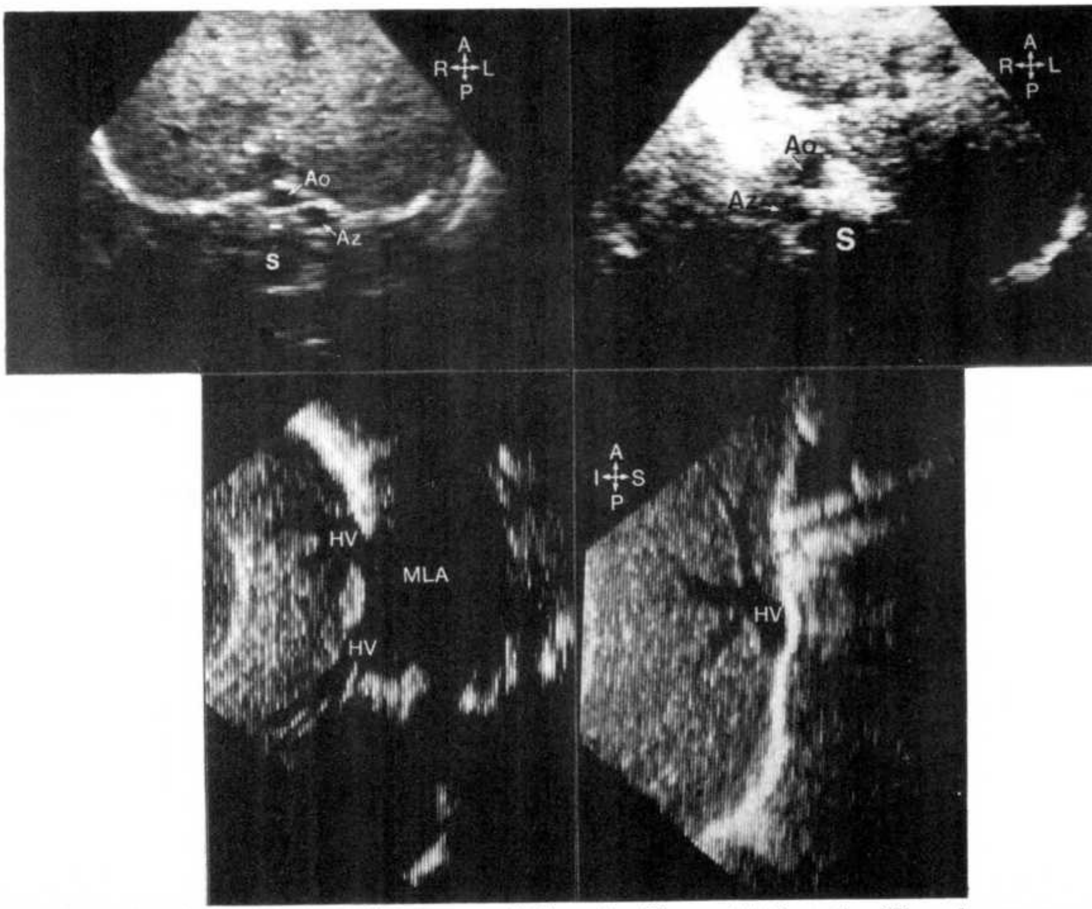


Fig. 4 *Two dimensional echocardiographic appearance of left isomerism. The aorta (Ao) is usually midline and an azygos continuation of the inferior vena cava (Az) is often present located posterior (P) either to the left (L) or the right (R) (upper panels). Total anomalous hepatic venous connection to a morphological left atrium (MLA) is present either as two separate hepatic veins (HV) (left lower panel) or a single vein (right lower panel).*

atria, but connected neither to the atria nor to any other vessels (Fig. 5). In all patients with left isomerism, including the two with the inferior vena cava entering the left or right sided atrium normally, one or two hepatic veins connected to the atrium separately from the other systemic venous return (Fig. 4 lower panels). The identity of the azygos continuation located posterior to the aorta was confirmed by echocardiographic contrast injection into the femoral vein in one patient.

NORMAL VS ABNORMAL SITUS

The wide range of congenital cardiac disease encountered in the 129 patients with situs solitus is shown in Table 2. These patients were compared with those with abnormal situs (inversus, right isomerism, or left isomerism) shown in Table 3. The ability of two dimensional echocardiography to separate these two groups is shown in Fig. 6 where abnormal situs is shown as a positive test and situs solitus as a negative test. There were no false negative diagnoses of abnormal situs and two false positives; these two patients both had exomphalos and malpositioned abdominal viscera. The usual pattern of situs solitus by two dimensional echocardiography was not present though atrial situs solitus was confirmed at necropsy in both. The intracardiac abnormalities were correctly predicted.

One patient had the typical symmetrical position of the inferior vena cava and aorta in the abdomen, but, in addition, a second venous structure was imaged to the right of and posterior to the aorta. This was cor-

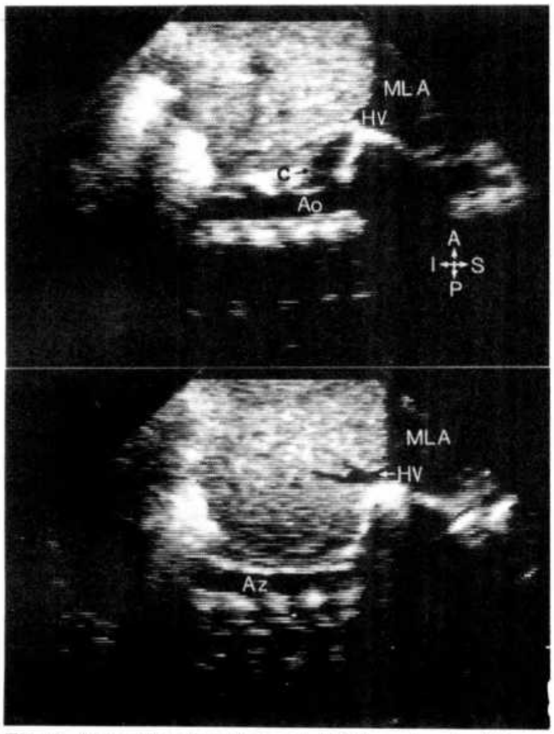


Fig. 5 *Long axis subcostal scans in left isomerism should identify the aorta (Ao), crus of the diaphragm (C), and hepatic venous connection (HV) to the morphological left atrium (MLA) (upper panel). Scanning laterally the azygos continuation of the inferior vena cava (Az) is visualised if present (lower panel).*

Table 2 *Two dimensional echocardiographic findings in 129 patients with situs solitus*

Apex		*Aortic arch*		
Left	*Right*	*Left*	*Right*	
126	3	120	9	
Atrioventricular connection		*Univentricular*		
Concordant	*Discordant*	*2 AV valves*	*Absent connection*	*CAVO*
114	1	3	10	1
Ventriculoarterial connection				
Concordant	*Discordant*	*DORV*	*Single outlet*	
88	26	9	6	

Isolated VSD, 31; persistent ductus arteriosus, 17 (isolated in eight); tetralogy of Fallot, 12; TAPVC, 10; DORV, 9; pulmonary stenosis, 8; aortic stenosis, 7; atrioventricular septal defect, 4; others, 15.

Abbreviations: AV, atrioventricular; CAVO, common atrioventricular valve orifice; DORV, double outlet right ventricle; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect.

rectly predicted as situs solitus with right azygos continuation of the inferior vena cava plus the normal inferior vena cava to right atrial connection and was confirmed by angiography and at surgery.

Dextrocardia was present in three patients with situs solitus and six patients with abnormal situs. This did not present any difficulty in the segmental approach to diagnosis by two dimensional echocardiography. Care was necessary, however, to trace the inferior vena cava to right atrial connection correctly.

The liver was lateralised to the right in all patients with situs solitus except the two patients with exomphalos.

ABNORMAL SITUS

There were 29 patients with abnormal situs including four with situs inversus, nine with right isomerism, and 16 with left isomerism. The two dimensional echocardiographic criteria which could be easily obtained in all patients were analysed for the ability to separate the three types of abnormal situs.

HEPATIC POSITION

The hepatic position was lateralised in all with situs inversus (to the left), but did not discriminate left from right isomerism (Table 4).

A midline liver was present in 18 patients with atrial isomerism (72%).

SYSTEMIC VENOUS RETURN

Although *azygos continuation* was present in one patient with situs solitus and is not the *sine qua non* of left isomerism, it was present in all but two patients (right sided in five, left sided in eight, and bilateral in one) (Table 5).

In the patient with left isomerism and bilateral azygos continuation the short axis scan of the abdomen showed the aorta to be midline with a posterior azygos vein on the left, an additional venous structure to the right, and no normal inferior vena cava entering the atrium. The azygos continuation could be traced to the junction with the ipsilateral superior vena cava or atrium in only two patients (Fig. 7).

The types of *hepatic venous connection* (Table 6) encountered were as follows.

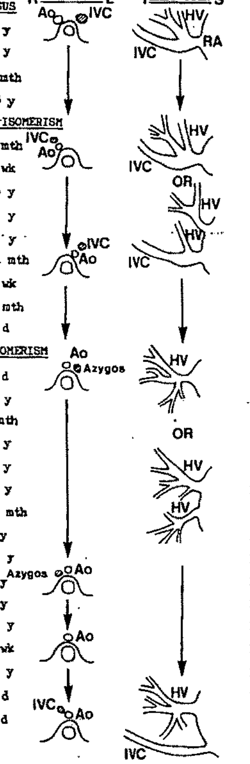
(1) Normal, with the hepatic veins connecting to the inferior vena cava at or near the entry into the right atrium,

(2) Normal connection of some hepatic veins to the inferior vena cava with separate connection of other hepatic vein(s) directly to an atrium (partial anomalous hepatic venous connection) or,

(3) Separate hepatic venous connection directly to an atrium via one or more veins (total anomalous hepatic venous connection).

All of the patients with right isomerism had connection of some or all of the hepatic veins to the inferior vena cava which then connected to the right sided atrium while all of those with left isomerism had total anomalous hepatic venous connection. In the patients with a common atrium or only a small remnant of

Table 3 *Two dimensional echocardiographic findings in 29 patients with abnormal situs*

	Sex	Age	Subcostal short axis scan	Subcostal long axis scan	Apex	AV connection	VA connection	Aortic Arch	Azygos continuation	HVC	SVC	PVC	Atrial Septum	Liver Position	Other
	INVERSUS														
1	M	6 y			R	Concordant	Discordant	R	No	N	L	N	Intact	L	VSD-Inlet PM
2	M	8 y			R	UV-Absent L connection	DOMC	R	No	N	L	N	ASD	L	
3	M	3 mth			R	Concordant	Concordant	L	No	N	L	N	ASD	L	VSD-Inlet PM
4	M	13 y			L	UV-Absent L connection	Discordant	R	No	N	L	N	ASD	L	
	RIGHT-ISOMERISM														
5	F	2 mth			L	UV-CAVO	DOMC	L	No	N	Bilat	"N"	SR	ML	PDA
6	M	1 wk			L	UV-CAVO	DOMC	R	No	N	R	"N"	Strand	ML	PS
7	M	16 y			L	UV-CAVO	Single outlet	R	No	N	ND	"N"	SR	ML	PA
8	F	9 y			L	Ambiguous/AVD	DORV	R	No	N	R	"N"	SR	L	VSD, PS
9	M	3 y			L	UV-CAVO	DOMC	R	No	N	R	PAPVC	CA	ML	PS
10	M	12 mth			L	Ambiguous	DORV	L	No	N	R	TAPVC-RA	CA	ML	PS
11	M	6 wk			L	Ambiguous/AVD	Discordant	L	No	PAHVC	R	"N"	CA	ML	PA
12	F	30 mth			R	UV-CAVO	Single outlet	R	No	N	Bilat	"N"	Strand	ML	PA
13	M	1 d			L	UV-CAVO	Single outlet	L	No	N	R	"N"	SR	ML	PS
	LEFT ISOMERISM														
14	F	1 d			L	Ambiguous	DORV	L	L	TAHVC (2veins)	Bilat	PAPVC	Intact	ML	PS-severe
15	F	17 y			L	Ambiguous	DORV	R	L	TAHVC	L	TAPVC-LSVC	ASD	ML	VSD-Inlet PM
16	F	4 mth			R	Ambiguous/AVD	DORV	L	L	TAHVC	Bilat	N	CA	ML	
17	M	8 y			R	Ambiguous	Concordant	R	L	TAHVC	L	N	ASD	ML	VSD-Inlet
18	M	7 y			R	Ambiguous	Concordant	R	L	TAHVC	L	N	Intact	R	Subaortic stenosis
19	F	6 y			L	Ambiguous	Concordant	L	L	TAHVC	Bilat	N	ASD	ML	
20	F	12 mth			L	Ambiguous	Concordant	L	L	TAHVC	Bilat	N	ASD	ML	LSVC-CS
21	M	3 y			L	Ambiguous	Concordant	L	Bilat	TAHVC	Bilat	N	Intact	R	VSD, SubAo. stenosis, PS, LSVC-CS
22	F	10 y			L	Ambiguous/AVD	Concordant	L	L	TAHVC	Bilat	N	SR	ML	Double orifice mitral valve
23	M	9 y			L	Ambiguous	Concordant	L	R	TAHVC	R	N	Intact	ML	VSD
24	M	5 y			L	Ambiguous/AVD	Concordant	R	R	TAHVC (2veins)	Bilat	PAPVC	SR	L	Tetralogy
25	F	14 y			L	Ambiguous	DORV	L	R	TAHVC	R	PAPVC	Intact	ML	VSD
26	M	6 wk			L	Ambiguous/AVD	Discordant	L	R	TAHVC	R	PAPVC	CA	ML	Necropsy
27	F	15 y			L	Ambiguous/AVD	Discordant	L	R	TAHVC	R	N	SR	ML	Double orifice mitral valve
28	M	1 d			L	Ambiguous	Single outlet	R	No (LIVC)	TAHVC (2veins)	L	N	ASD	ML	VSD, PA - necropsy
29	F	1 d			L	Ambiguous/AVD	DORV	L	No (RIVC)	TAHVC	Bilat	PAPVC	CA	ML	PS - necropsy

Abbreviations: Ao, aorta; AVD, atrioventricular septal defect (partial or complete); ASD, atrial septal defect at fossa ovalis; Bilat, bilateral; CA, common atrium; CAVO, common atrioventricular valve orifice; CS, coronary sinus; DOMC, double outlet main chamber; DORV, double outlet right ventricle; d, days; F, female; I, inferior; IVC, inferior vena cava; L, left; LIVC, left inferior vena cava; LSVC, left superior vena cava; M, male; ML, midline; mth, months; ND, not defined; N, normal; PAHVC, partial anomalous hepatic venous connection; PAPVC, partial anomalous pulmonary venous connection; PA, pulmonary atresia; PM, perimembranous; PVC, pulmonary venous connection; R, right; RIVC, right inferior vena cava; S, superior; SR, superior rim of interatrial septum; TAHVC, total anomalous hepatic venous connection; TAPVC, total anomalous pulmonary venous connection; UV, univentricular atrioventricular connection; VSD, ventricular septal defect; wk, weeks; y, years; "N", total anomalous pulmonary venous connection to a confluence which communicates directly with the left sided atrium in right isomerism.

atrial septum secundum it was difficult confidently to assign the hepatic venous connections to the right sided or left sided atrium.

Superior systemic venous connections (Table 7) were imaged in all patients. Bilateral superior venae cavae were present in 14 of the patients with atrial isomerism (43%). In the patient with bilateral azygos continuation, the left superior vena cava received the azygos vein and then drained to the coronary sinus, whereas the right superior vena cava entered the right atrium directly.

In three of the 10 patients with bilateral superior vena cava, no bridging innominate vein was identified by two dimensional echocardiography or angiography.

A *coronary sinus* was identified by two dimensional echocardiography in all of the patients with situs inversus and in three patients with left isomerism (Fig. 8), two with a left superior vena cava connecting it.

PULMONARY VENOUS CONNECTION

Patterns of partial and total anomalous pulmonary venous connection were identified in the patients with atrial isomerism as well as in the normal subjects (Fig. 9). Normal connection was present in all four patients with situs inversus (Table 8).

Seven patients with right isomerism had a pattern of total anomalous pulmonary venous connection to a confluence which connected directly to the left sided atrium, two had pulmonary veins connecting to both atria, and one had total anomalous pulmonary venous connection to the right sided atrium. Ten of the patients with left isomerism had an entirely normal

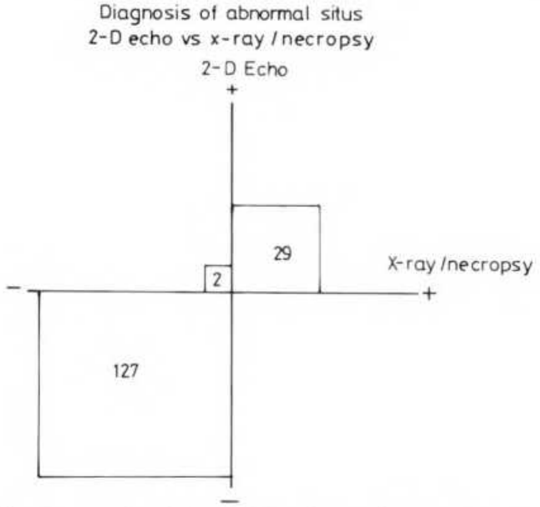


Fig. 6 *Detection of abnormal situs by two dimensional echocardiography (2-D echo) compared with high kilovoltage chest* x-ray *necropsy findings. Twenty nine patients had abnormal situs (true positives) and 127 had situs solitus (true negatives). The two false positives were in patients with exomphalos and displacement of the abdominal viscera. Abnormal situs = a positive test.*

Table 4 *Hepatic position*

	Right	*Left*	*Midline*	*Totals*
Inversus	0	4	0	4
Right isomerism	2	2	5	9
Left isomerism	2	1	13	16

Table 5 *Azygos continuation*

	None	*Unilateral*	*Bilateral*	*Totals*
Inversus	4	0	0	4
Right isomerism	9	0	0	9
Left isomerism	2	13	1	16

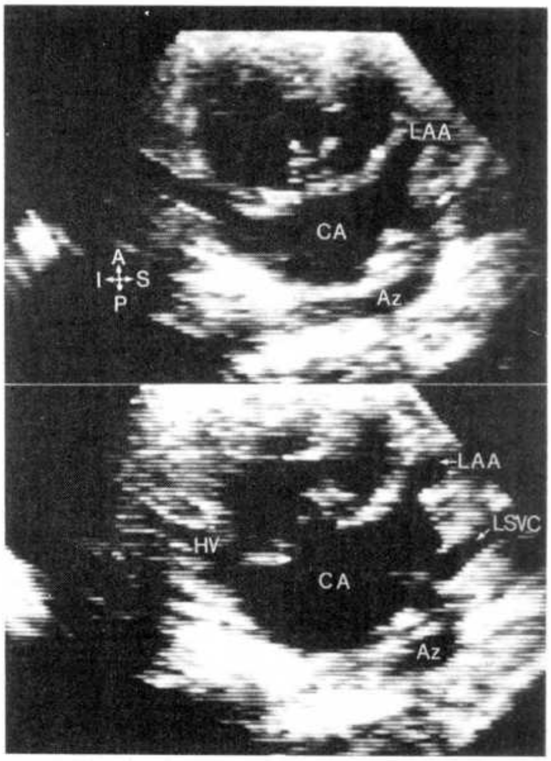


Fig. 7 *Identification of azygos connection in a 3-month-old girl with left isomerism and a common atrioventricular valve orifice and common atrium (CA). The azygos (Az) joins the left superior aspect of the common atrium. A left superior vena cava (LSVC) enters separately (lower panel). Note the left atrial appendage (LAA) and hepatic venous connection (HV).*

Table 6 *Heptic venous connection*

	Normal	*PAHVC*	*TAHVC*	*Totals*
Inversus	4	0	0	4
Right isomerism	8	1	0	9
Left isomerism	0	0	16	16

PAHVC, partial anomalous venous connection (not all hepatic veins connect to the inferior vena cava); TAHVC, total anomalous hepatic venous connection.

pulmonary venous connection. Thus, pulmonary venous connection did not aid in situs identification, though connection of pulmonary veins to a confluence behind the heart, and thence to a left sided atrium, should suggest right isomerism.

ATRIAL SEPTUM MORPHOLOGY

There were five patterns of atrial septum morphology which could be readily identified in patients with abnormal situs (Table 9; Fig. 10).

The atrial strand seen in two patients with right isomerism is frequently found with this type of situs.[13]

We have succeeded in visualising the atrial appendages in some neonates (Fig. 11), including one patient with left isomerism. The recognition, however, of distinctive atrial appendage characteristics *routinely* is not yet feasible non-invasively.

Table 7 *Superior systemic venous connections*

	RSVC	*LSVC*	*Bilateral SVC*	*Totals*
Inversus	0	4	0	4
Right isomerism	3	0	6	9
Left isomerism	4	4	8	16

LSVC, left superior vena cava only; RSVC, right superior vena cava only; Bilateral SVC, superior vena cavae on the left and right with or without a bridging innominate vein.

Discussion

The sequential method of classifying congenital heart disease introduced by Van Praagh *et al.*[2] is based on a knowledge of atrial situs. This approach has been extended from descriptions of pathological material to the diagnosis of cardiac abnormalities diagnosed preoperatively. Angiography has been used to do this in the past and the separation of atrial situs into solitus, inversus, and ambiguus has been attempted.[14 15] The close correlation of bronchial and atrial situs has allowed situs to be determined with a chest radiograph though special techniques are necessary in infants and young children.[10]

M-mode echocardiography has been applied to sequential cardiac diagnosis[16 17] but is severely limited and of no use in determining atrial situs.

Many correlates exist which might be used to predict the atrial situs. These include: (1) *splenic status*[6 18]; (2) *lung lobation*; (3) *position of abdominal viscera*, which has been shown to lack accuracy[13]; (4) *bronchial morphology* which has a high correlation with atrial situs[13 19] and has the advantage of being non-invasive.

Other correlates which have been studied include: (5) *pulmonary venous connection*; (6) *presence or absence of coronary sinus*[13]; (7) *pulmonary artery morphology*[9]; (8) *systemic venous connection*[14]; and (9) *electrocardiogram P wave axis.*[20] Becker and Anderson[21] suggested that, (10) *hepatic atrial connection* may be uniform in right isomerism. Elliott *et al.*[22] showed that forward venous angiography was valuable in diagnosing right isomerism and described (11) *position of the inferior vena cava and aorta* as "the aorta seeking out" the inferior vena cava in the abdomen.

Two dimensional echocardiography is an excellent method of imaging intra- and extracardiac thoracic structures and is equally suited for displaying denser structures such as the liver. Therefore, we used two dimensional echocardiography to assess (3), (5), (6), (8), (10), and (11) to predict atrial situs thereby.

This investigation extends the non-invasive diagnosis of situs in two important directions. Firstly, the position of the inferior vena cava and aorta alone has been shown reliably to separate those patients with situs solitus from those with either situs inversus or atrial isomerism (situs ambiguus) and to be specific for situs inversus. Right isomerism has a typical pattern by two dimensional echocardiography using this criterion and would have been adequate on its own apart from one exception in this study. All previous detailed studies of situs have lacked information concerning the *in vivo* position of the great vessels in the abdomen. Tomographic methods such as computerised tomographic scans and two dimensional echocardiography now allow non-invasive determination of these details which have previously been recognised to be important indicators of situs.[22]

The level of the diaphragm (approximately T10) is an important location for making these observations. Between the level of the renal veins and this location the suprarenal segment of the inferior vena cava (deriving from the subcardinal system) normally connects to the hepatic veins and the atrium. If there is

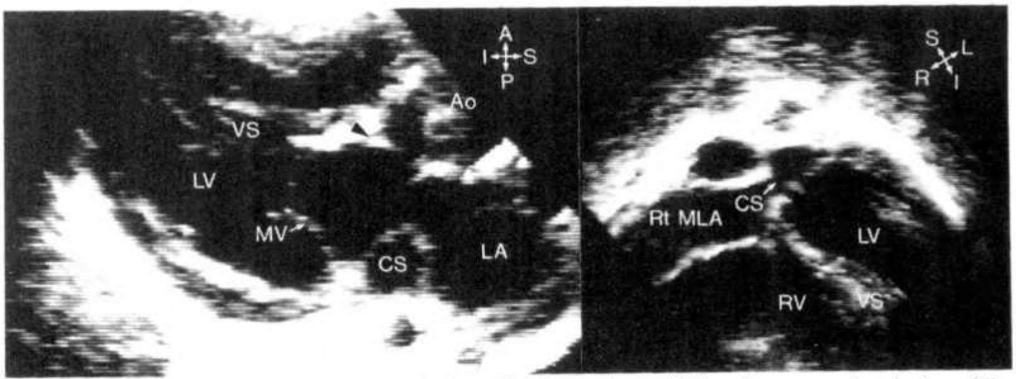


Fig. 8 *Dilated coronary sinus (CS) in a 3-year-old boy with left isomerism and bilateral azygos continuation (case 21). Note the presence of subaortic stenosis (left panel). The coronary sinus to right sided morphological left atrium (Rt MLA) junction (right panel) was present and did not aid in separating left isomerism from situs solitus. LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle; VS, ventricular septum.*

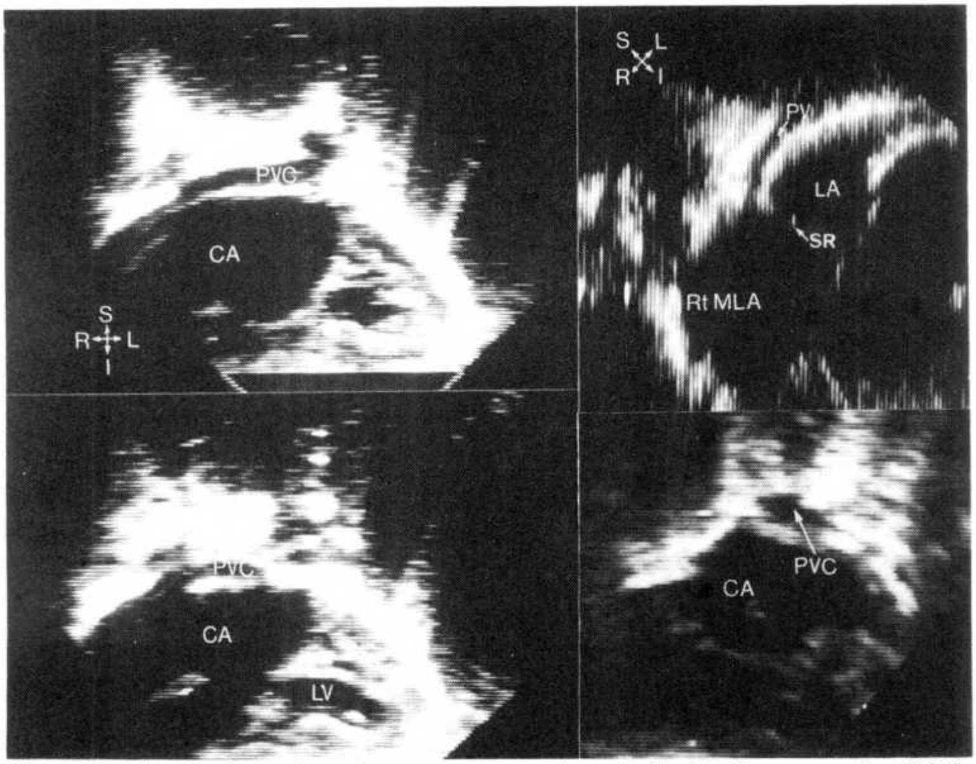


Fig. 9 *Examples of total anomalous pulmonary venous connection to the right side of a common atrium (CA) in right isomerism (left upper and lower panels). Partial anomalous pulmonary venous connection of the left pulmonary veins (PV) to the right atrium in left isomerism (right upper panel). A pulmonary venous confluence (PVC) (right lower panel) was present in many patients with right isomerism even when the drainage was to the left sided atrium. Rt MLA, right sided morphological left atrium; SR, superior rim; LV, left ventricle.*

Table 8 *Pulmonary venous connection*

	Normal	*PAPVC*	*TAPVC*	*Totals*
Normal	4	0	0	4
Right isomerism	0	1	8*	9
Left isomerism	10	5	1	16

*Seven connecting to left sided morphological right atrium. PAPVC, partial anomalous pulmonary venous connection; TAPVC, total anomalous pulmonary venous connection.

azygos continuation of the inferior vena cava (deriving from the supracardinal system) it will often enter the thorax with the aorta through the aortic hiatus of the diaphragm.[23] The azygos continuation was detected at this level in nearly all patients in this study.

Secondly, the patterns of the inferior vena cava connection to the atrium and hepatic venous connection aided in separating the rare patient with situs solitus and azygos continuation from those with left isomerism. In addition, though two patients with left isomerism had no azygos continuation and the aorta and inferior vena cava ran together in one, there was a totally separate hepatic venous connection. Therefore, total anomalous hepatic venous connection was specific for left isomerism.

The complexity of the systemic venous anomalies in atrial isomerism serves to support the view that not all patients fall into the category of either solitus or inversus. These data strongly support the view that there are four types of situs and that certain aspects of systemic venous return are typical for each type including those with atrial isomerism. For example, all patients with right isomerism had at least a right superior vena cava plus a normal "right" type of hepatic venous and inferior vena cava to right atrial connection. Partial anomalous hepatic venous connection is known to occur in right isomerism[13] and was present in one patient, but total anomalous hepatic venous connection was not seen. We have observed that the hepatic venous morphology is typical of a right hepatic vein in right isomerism, situs solitus, and situs inversus but is atypical in left isomerism.

Table 9 *Atrial septum morphology*

	PFO/intact	*Secundum ASD*	*Common atrium*	*Superior rim*	*Strand*	*Totals*
Inversus	1	3	0	0	0	4
Right isomerism	0	0	3	4	2	9
Left isomerism	5	5	3	3	0	16

ASD, atrial septal defect; PFO, patent foramen ovale, Common atrium, superior rim, and strand all occurred with atrioventricular septal defects.

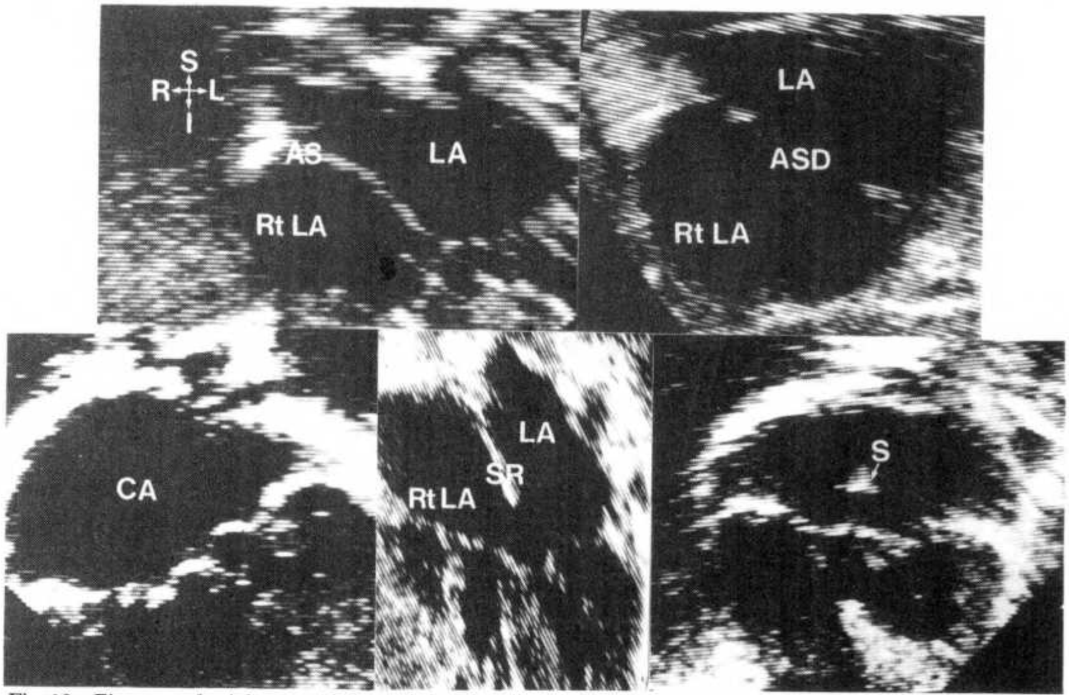


Fig. 10 *Five types of atrial septum (AS) morphology found in atrial isomerism. Intact septum (left upper), secundum atrial defect (ASD) (right upper), common atrium (CA) (left lower), superior rim (SR) of atrial septum (middle lower), and strand (S) (right lower). LA, left atrium; Rt LA, right sided morphological left atrium.*

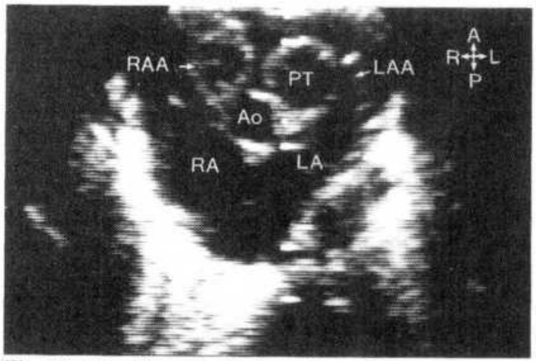


Fig. 11 *Two dimensional echocardiographic appearance of atrial appendages in situs solitus. Note the broad, blunt appearance of the right atrial appendage (RAA) and narrow pointed appearance of the left atrial appendage (LAA). PT, pulmonary trunk.*

We do not know if all patients with situs solitus and azygos continuation also have a small or rudimentary remnant of inferior vena cava which connects in the normal way after receiving hepatic venous connection. The patient shown in Fig. 12 with situs solitus and a normal inferior vena cava together with hemiazygos continuation illustrates this possibility. Though we have not examined this patient by two dimensional echocardiography this represents one situation where subcostal scans should identify the inferior vena cava but, if it were hypoplastic, a false positive diagnosis of left isomerism might be made. We continue to use the high kilovoltage chest radiograph to diagnose situs in such questionable cases.

The prevalence of abnormalities of situs is not well defined because not all are associated with congenital cardiac defects which, in the past, have led to investigative procedures. Based on the knowledge we have

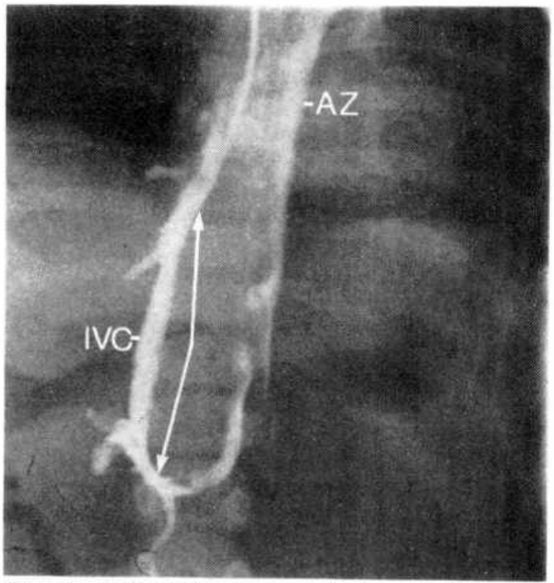


Fig. 12 *Angiographic appearance of suprarenal inferior vena cava (IVC) (arrows) and hemiazygos continuation of the IVC (AZ) in a patient with situs solitus. Atresia or severe hypoplasia of the region indicated could mimic left isomerism.*

gained in this investigation we would predict that more cases of abnormal situs will be recognised with the aid of two dimensional echocardiography. Two patients in the series whose situs was thought to be solitus have been followed in our clinic for relatively minor congenital defects. One had had previous angiography and open heart surgery yet filter films of both bronchi showed left isomerism in both. Comparing previously reported pathological series of isomerism, one finds a ratio of nearly 3:1 for right/left isomerism in necropsy material, whereas the ratio is nearly reversed when the diagnosis is made before death. This suggests that the prevalence of left isomerism is much higher than right isomerism, as found in life by Partridge *et al.*[8] and Deanfield and colleagues.[10] This undoubtedly reflects the poorer prognosis of right isomerism, and the resultant higher incidence of hospital necropsy.

We suggest a two dimensional echocardiographic approach to the diagnosis of situs as outlined in Fig. 13. Assessment of the aorta/inferior vena cava relation in the subcostal position immediately separates those patients with symmetric appearance of the great vessels, who have situs solitus or inversus, from those with an abnormal appearance. If the aorta and inferior vena cava run together, then atrial isomerism is almost certainly present unless some other condition such as exomphalos exists to disturb abdominal great vessel relations. Long axis subcostal views are then used further to identify the venous structures and to examine the hepatic venous connection. If there is total anomalous hepatic venous return, the diagnosis is left isomerism. Most of these patients will have an interrupted inferior vena cava. If there is not total anomalous hepatic venous return the diagnosis is almost certainly right isomerism or lateralised situs, which are distinguished as already described. Further studies in a larger number of patients will be required to answer the question of whether the hepatic veins ever connect to the inferior vena cava in patients with left isomerism. If only the aorta can be visualised and the hepatic veins all appear to connect anomalously, then the most likely diagnosis is left isomerism with azygos continuation, though we would use the bronchial morphology as an aid in such circumstances.

We thank Dr F Arensman, Harefield Hospital, for permission to examine case 4.

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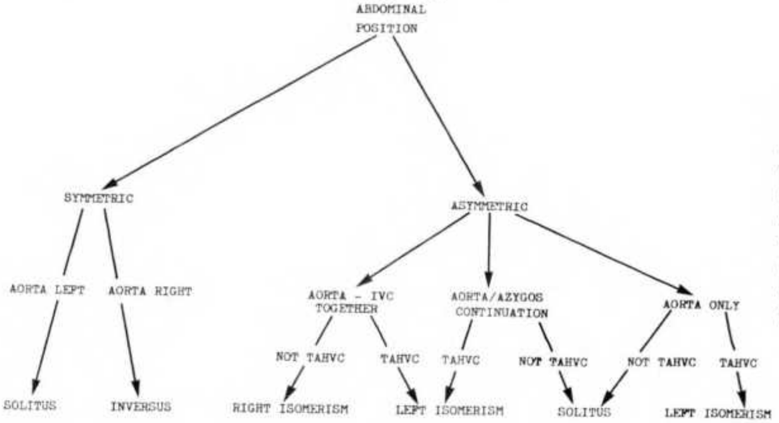

Fig. 13 *Two dimensional echocardiographic approach to the diagnosis of situs based on long and short axis subcostal views. Abnormal situs is detected by the asymmetry of the short axis view and further delineation is possible based on the presence or absence of total anomalous hepatic venous connection (TAHVC).*

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Isolated anterior mitral cleft

Two dimensional echocardiographic assessment and differentiation from "clefts" associated with atrioventricular septal defect

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SUMMARY Five patients with isolated clefts in the anterior leaflet of the mitral valve, unassociated with atrioventricular septal defects, are described. All had significant mitral regurgitation, with the cleft being the only abnormality in three. Two patients had an associated ventricular septal defect, one with a straddling right atrioventricular valve. Angiocardiography in four showed moderate regurgitation, but was not able to delineate the aetiology. Two dimensional echocardiography showed a constant defect in the anterior leaflet, pointing towards the left ventricular outflow tract. This differed from 30 cases with atrioventricular septal defects where the "cleft" pointed towards the interventricular septum and was situated between the anterior and posterior bridging leaflets. All cases with isolated clefts had surgical correction, with minimal residual regurgitation on follow-up examination in two cases. Our current policy in patients with uncomplicated isolated cleft involves non-invasive assessment of these children and surgical correction if the regurgitation is significant.

Most cardiologists and surgeons have adopted a conservative approach to the child with mitral regurgitation. This is justified as the prospect of mitral valve replacement in this age group is not to be considered lightly, in view of the problems associated with prosthetic valves.[1] Reconstructive surgery may prove to be possible, but usually this cannot confidently be decided before operation on the basis of traditional investigational techniques. So the child goes for operation in an atmosphere of uncertainty, with all those involved hoping, but usually not knowing, that reconstructive surgery will be possible.

Part of the basis for uncertainty is the wide variability of anatomical substrates for congenital mitral regurgitation. This may be produced by redundant and deficient chordae tendineae, parachute mitral valve and its variants, anomalous mitral arcade, floppy mitral valve, and, rarely, Ebstein's anomaly of the mitral valve.[2 3]

An isolated cleft in the anterior (aortic) leaflet of the mitral valve is an uncommon cause of regurgitation, the cleft always pointing towards the left ventricular outflow tract. But it is an important lesion because it is potentially correctable.[4]

In the past, M-mode echocardiography has provided functional information about mitral regurgitation, but apart from mitral valve prolapse has yielded little morphological detail as to the exact nature of the lesion.[5] Angiocardiography has permitted recognition of some specific varieties of congenital mitral valve disease, but has proved singularly unsuccessful in the recognition of isolated mitral cleft.[6] In contrast, two dimensional echocardiography should enable recognition of an isolated cleft.

We have treated a group of children where the mitral regurgitation was the result of a localised cleft in the anterior leaflet, unassociated with atrioventricular septal defects. We now describe their preoperative assessment, surgical management, and our current approach to the problem.

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Subjects and methods

All patients with isolated anterior mitral clefts attended the congenital heart clinics of The Hospital for Sick Children, Great Ormond Street, or the National Heart Hospital, Westmoreland Street. In all cases a clinical diagnosis of mitral regurgitation had been made and radiological evidence of left ventricular enlargement was present. Of the five patients studied, four had angiocardiographic evidence of moderate to severe mitral regurgitation. The fifth patient, in view of our previous experience, was submitted to operation without prior invasive studies. Two cases had an associated ventricular septal defect, one with a straddling right atrioventricular valve diagnosed by echocardiography. In the others, the anterior mitral cleft was an isolated defect.

All patients had both M-mode and two dimensional echocardiographic assessments. The patients were studied with either an Advanced Technology Laboratory mechanical sector scanner using a 3·0 MHz transducer, or a Smith Kline mechanical scanner with a 2·25 MHz scan head. The apical and subcostal four chamber views were used to assess the leaflets, as was the short axis view at the level of the aortic root. In the latter cut, a scan from the aortic root to the apex of the left ventricle enabled an accurate assessment of the anterior and posterior mitral leaflets and associated papillary muscles.

In all patients M-mode studies were performed to assess the mitral valve motion and left ventricular cavity size. Two cases had preoperative, and three postoperative pulsed Doppler studies performed by sampling in the left atrium. All were submitted for surgical repair of the cleft anterior mitral leaflet.

To clarify the difference between an isolated anterior mitral cleft and that associated with an atrioventricular septal defect, a further group of 30 patients with the latter abnormality was included in the study. All of these patients had either angiocardiographic or surgical confirmation of the defect.

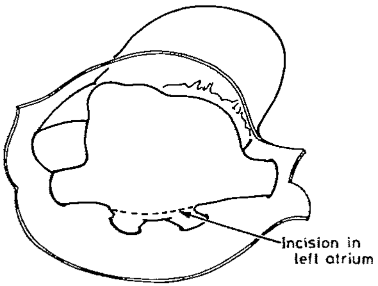
PREOPERATIVE ECHOCARDIOGRAPHIC STUDIES

Patients with an isolated mitral cleft

In all cases there was a localised cleft in the anterior (aortic) leaflet of the mitral valve (Fig. 1 and 2). This was best appreciated in a short axis scan from the aortic root to the apex of the left ventricle. Just below the aortic root, a position is obtained wherein the left ventricular outflow tract and the area of aortic to mitral valvar fibrous continuity can be visualised. When the mitral valve is normal, the anterior leaflet is seen as a continuous dense echo (Fig. 3), but in patients with an anterior cleft there is a break in this echo (Fig. 4). In all cases the edges of the cleft appeared as denser echoes suggesting that they were rolled and thickened, this observation being confirmed at operation (Fig. 4). During real-time study, an abnormal pattern of movement of the anterior leaflet existed throughout the assessment. So, during systole the two portions of the anterior leaflet floated together, whereas during diastole, the edges of the cleft parted widely. Most importantly, the cleft extended into the area of aortic-mitral continuity, and was not directed towards the interventricular septum. All cases had two papillary muscles with no other abnormality of the mitral valve being seen. In particular, the chordae from the anterior mitral leaflet were normally situated.

In the apical four chamber view the effective mitral orifice is frequently not visualised, as the anterior mitral leaflet crosses the plane of the transducer beam before inserting into the posteromedial papillary muscle group. When a localised anterior cleft is present, an echo free area is readily visualised in this cut, representing the break in the leaflet. This appearance can also be visualised in the subcostal four chamber view (Fig. 5).

In all cases the inferior limbus of the interatrial septum was intact, and there was a normal atrioventricular muscular septum (Fig. 5). Thus, the atrioventricular valves were in all cases attached to the septum



Surgeon's eye view of left atrioventricular valve
via left atrial incision

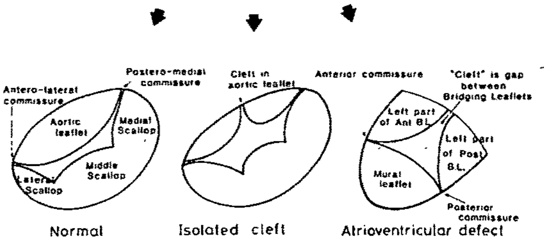


Fig. 1 *A diagrammatic representation of the surgeon's view of the left atrioventricular valve via a left atrial incision. Note the difference between the cleft in a normal anterior mitral leaflet as compared with the "cleft" seen in an atrioventricular septal defect. In the latter case the "cleft" exists between the anterior and posterior bridging leaflets.*

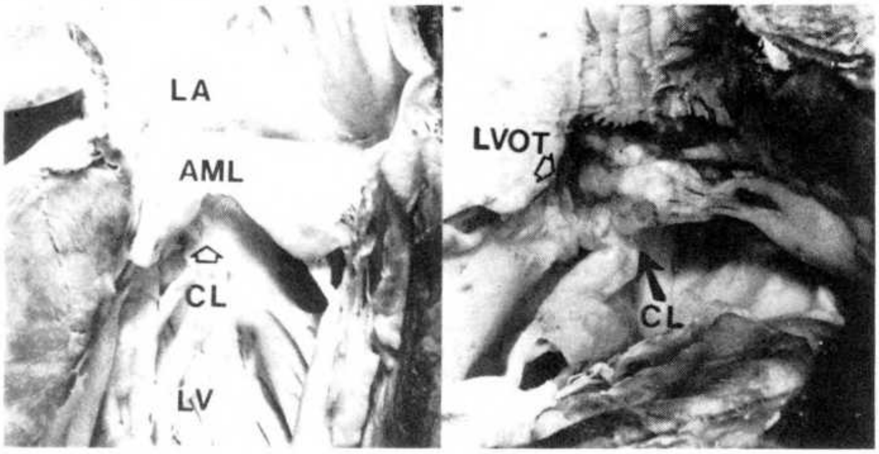


Fig. 2 *Necropsy specimen from a patient with an isolated cleft in the anterior mitral leaflet. The picture on the left shows the cleft anterior leaflet. The picture on the right shows the cleft pointing towards the left ventricular outflow tract. AML, anterior mitral leaflet; CL, cleft; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract. This figure is reproduced by kind permission of Professor Anton Becker, Amsterdam.*

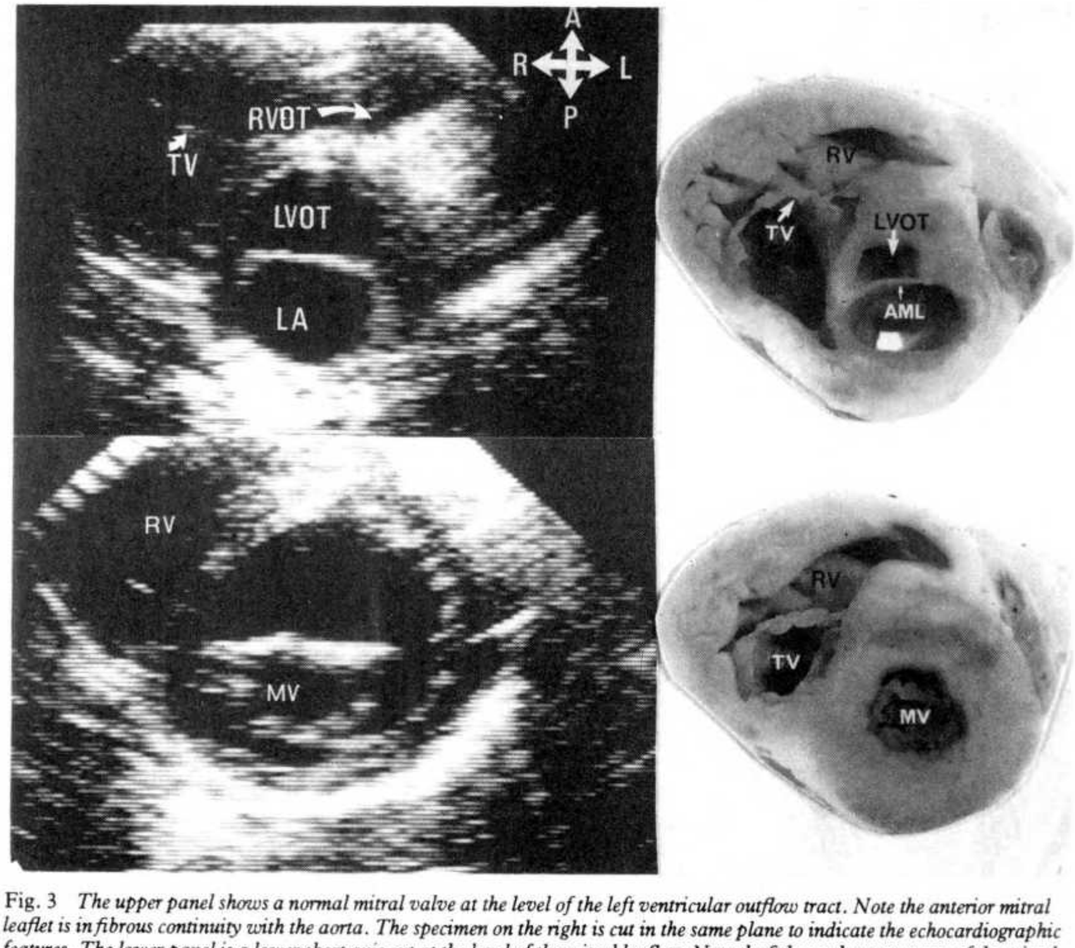


Fig. 3 *The upper panel shows a normal mitral valve at the level of the left ventricular outflow tract. Note the anterior mitral leaflet is in fibrous continuity with the aorta. The specimen on the right is cut in the same plane to indicate the echocardiographic features. The lower panel is a lower short axis cut at the level of the mitral leaflets. Note the fishmouth appearance of the mitral valve. The specimen on the right is cut on the same plane as the echocardiogram. MV, mitral valve; RV, right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve. See Fig. 2 for remaining abbreviations.*

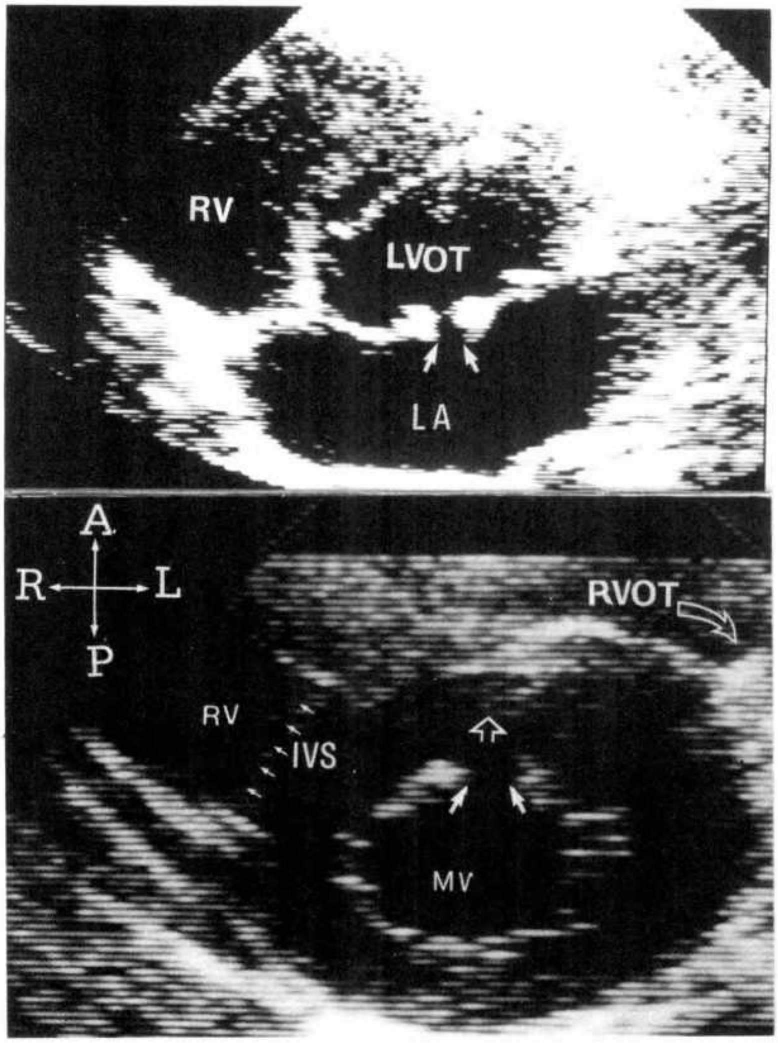


Fig. 4 *The top picture is a short axis cut at the level of the left ventricular outflow tract in a patient with an isolated cleft in the anterior mitral leaflet. Note the cleft, indicated by the two arrows pointing towards the outflow tract, and not the right ventricle. The lower picture is a short axis cut at the level of the mitral valve. Note again the cleft indicated by the arrows, pointing towards the outlet of the heart and not the right ventricle. IVS, interventricular septum. See Fig. 2 and 3 for remaining abbreviations.*

at different levels, with the tricuspid valve being attached more inferiorly. The membranous and inlet septa were intact in all patients, including the one with a ventricular septal defect and straddling right (tricuspid) atrioventricular valve. Surprisingly, the defect in the latter patient was found to be in the muscular trabecular septum with chordae from the septal tricuspid leaflet straddling to be attached in the morphologically left ventricle. In this case, previously described,[7] a posterior interventricular septum going to the crux was present. In the other case the defect was perimembranous. M-mode assessments of the mitral valve showed a normal "M" shaped pattern with some associated fluttering of the anterior leaflet during diastole. The remaining features were those of atrial and ventricular enlargement.

The left ventricular end-diastolic volume was greater than two standard deviations above the mean for age in every case and the left atrial size was also significantly increased.

Patients with atrioventricular septal defects

In all cases the short axis cut showed that the "cleft" was situated between the anterior and posterior bridging leaflet pointing towards the interventricular septum and not the left ventricular outflow tract (Fig. 6).

INTRAOPERATIVE FINDINGS AND MANAGEMENT OF ISOLATED MITRAL CLEFTS

All patients were operated on cardiopulmonary bypass, with moderate hypothermia and cold cardioplegia. The left atrium was opened posterior to the

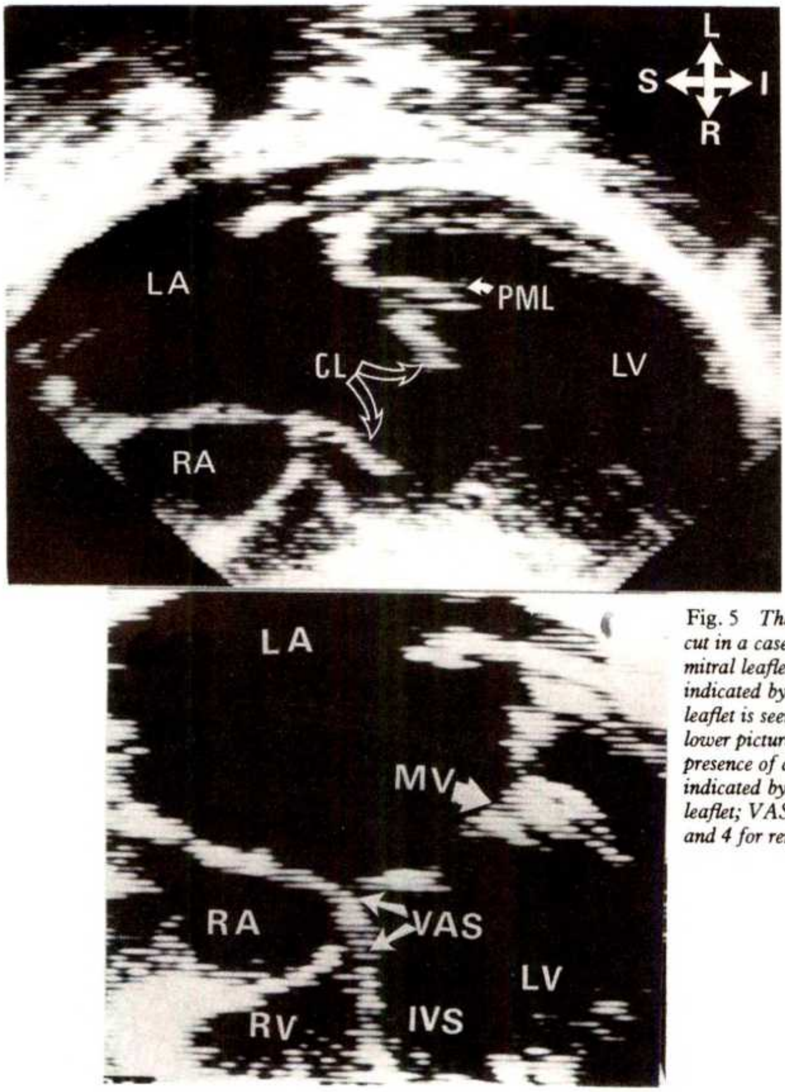


Fig. 5 *The upper panel is a subcostal four chamber cut in a case with an isolated cleft in the anterior mitral leaflet. Note the division in the anterior leaflet indicated by the two arrows. The posterior mitral leaflet is seen in the upper part of the picture. The lower picture is from the same patient showing the presence of an atrioventricular muscular septum indicated by the two arrows. PML, posterior mitral leaflet; VAS, ventriculoatrial septum. See Fig. 2, 3, and 4 for remaining abbreviations.*

Waterston groove. The mitral valve was tested by injecting cold saline under pressure into the left ventricular apical vent. The left atrium was moderately enlarged in all patients. A universal finding was a deep cleft in the anterior leaflet, pointing towards the aortic root and extending to the annulus (Fig. 1 and 2). The edges of the cleft were thickened and rolled. The anterior part of the leaflet had chordal attachments to the anterior papillary muscle. The subvalvular apparatus was normal in all patients.

The repair consisted in all cases of closing the cleft with interrupted sutures starting at the annulus and progressing towards the free edge of the valve. The regurgitation at operation was completely abolished in all cases but one, where a small central jet remained. In one patient in whom the regurgitation was abolished at operation, on follow-up there was a soft pansystolic murmur at the apex with no diastolic murmur. In these two patients pulsed Doppler ultrasound showed a regurgitant jet in the left atrium. Three of the patients had no residual murmur of mitral regurgitation, and this absence of regurgitation was confirmed in one patient by pulsed Doppler ultrasound.

In the patient with the trabecular ventricular septal defect and straddling right (tricuspid) atrioventricular valve, the defect was closed through the tricuspid valve, accepting a small defect around the papillary

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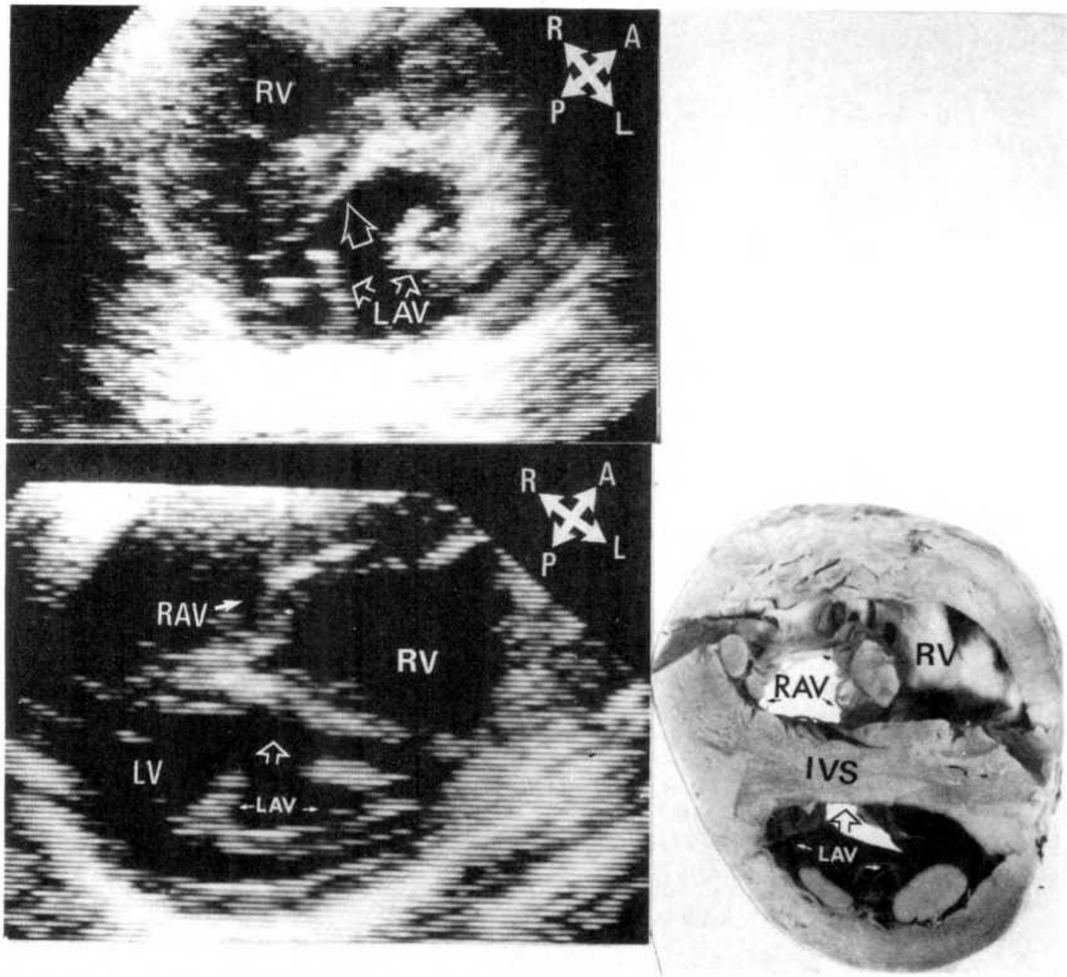

Fig. 6 *These pictures are from a case with an atrioventricular septal defect. The upper picture is a precordial short axis cut at a slightly higher level than that seen in the lower panel. Note that the "cleft" between the anterior and posterior bridging leaflets points towards the interventricular septum and not the outflow tract of the left ventricle. The bottom panel, at a lower level, again indicates the cleft between the leaflets pointing towards the interventricular septum. The specimen on the right is from a patient with an atrioventricular septal defect and partitioned orifices. The cut is in the same plane as the bottom left echocardiogram. Note the cleft, indicated by the arrow pointing towards the interventricular septum. LAV, left atrioventricular valve; RAV, right atrioventricular valve. For remaining abbreviations see Fig. 3 and 4.*

muscle attached to the left side of the septum.

Discussion

These findings throw light on two largely separate questions, one to do with descriptive anatomy and one clinical. Firstly, what is the difference between isolated cleft of the anterior mitral leaflet and the "mitral cleft" found in atrioventricular septal defects?

Secondly, how may patients with isolated cleft of the anterior mitral leaflet be distinguished from patients with mitral regurgitations from other causes?

CLEFTS AND ATRIOVENTRICULAR SEPTAL DEFECTS

The normal mitral valve consists of two leaflets, the anterior or aortic leaflet and the posterior or mural one. These are divided by the anterolateral and posteromedial commissures which are supported by paired left ventricular papillary muscles, the anterolateral and posteromedial group[8 9] (Fig. 1). "Clefts" are usually described as part of the anatomy of atrioventricular septal defects. In these cases, a normal mitral valve does not exist and the left sided valve is formed from components of three of the five basic leaflets, which may be found in all atrioventricular septal defects. The "left sided cleft" in such hearts actually lies between the anterior and posterior bridging leaflets as they insert along the crest of the interventricular septum[10] (Fig. 1 and 6).

Isolated clefts of the mitral valve are rare, but have previously been described in the anterior and posterior leaflets unassociated with atrioventricular defects.[4] The cleft usually involves the anterior leaflet and divides it in its entirety (Fig. 1). Anomalous chordal attachments are frequently a complicating feature though we found none in these patients. It must be stressed, however, that if the cleft involves the anterior leaflet and is to be regarded as isolated, it must point towards the left ventricular outflow tract. In those with an atrioventricular septal defect, because of the very nature of the leaflet pattern the "cleft" can in no sense divide the anterior leaflet[10] as an isolated mitral cleft does. And because it does not divide the anterior leaflet it points to the interventricular septum (compare Fig. 1, 4, and 6) rather than to the left ventricular outflow tract.[11]

These considerations lead us to suppose that, if the very rare conditions of atrioventricular septal defect with intact atrial and ventricular septa were encountered, the cleft in the "left atrioventricular valve" would still point towards the septum. Furthermore, the other echocardiographic stigmata of atrioventricular septal defects would still be present, notably the presence of two atrioventricular valves at the same level, resulting from absence of the atrioventricular septum.[12 13]

DIFFERENTIATION FROM OTHER MITRAL ANOMALIES, AND CONSEQUENCES FOR MANAGEMENT

Mitral valve abnormalities in young children are almost always of congenital origin, though mitral regurgitation may also be secondary to primary left ventricular disease, or to anomalous origin or atresia of the left main coronary artery. In older children, rheumatic mitral disease is more common. The echocardiographic features of congenital mitral stenosis have previously been described.[14 15] In patients in whom the predominant lesion is regurgitation, the majority have no gross malformation of the valve, but possess redundant leaflets and a dilated annulus. Others have grosser abnormalities such as single papillary muscles. Over the past few years, particularly since the advent of M-mode echocardiography, prolapse of the mitral leaflets has been suggested as a likely cause of this regurgitation. Normally the posterior leaflet is involved, but occasionally the anterior one is.[16 17]

The majority of children with gross structural abnormalities of the mitral valve who present in early childhood have associated defects which frequently mask the signs of mitral valve disease. Indeed, it is rare for them to have only isolated mitral regurgitation. In the older age group cardiac failure is rare and the lesion is usually detected during routine examination. Even though mitral regurgitation is severe, the combination of good left ventricular function and frequently massive left atrial enlargement ensure that patients maintain a relatively normal left atrial pressure and have little in the way of symptoms, at least in their first decade. Because the condition is well tolerated, and it has not been possible to guarantee that surgery will not involve mitral valve replacement, the tendency has been to postpone surgery until symptoms demand it. Cardiac catheterisation and angiocardiography have in our experience often not provided any more information than was obvious from clinical and non-invasive investigation.

We believe that these results show the possibility of a radical change in managment for at least one subgroup of patients with congenital mitral regurgitation. This is because two dimensional echocardiography provides the necessary detailed information as to the precise anatomical abnormalities of the leaflets and subvalvar apparatus. Such simple structural abnormalities as localised clefts are readily visualised. These patients can then be selected for early surgical repair on the basis that a good result can be anticipated, thereby avoiding the problems of left ventricular dysfunction which may supervene in patients with long standing mitral regurgitation.[18] We believe that these patients reflect the fact that the mitral regurgitation is largely, if not entirely, the result of the cleft. Repair of the cleft produces a normal or near normal anterior mitral leaflet (Fig. 7).

This situation is quite different from that pertaining to "left sided clefts" in atrioventricular septal defects. Here the "cleft" is but one cause of left atrioventricular valve regurgitation, and indeed may not cause any regurgitation at all. Repairing the "cleft" in no way restores a normal "anterior mitral leaflet", and may actually result in left ventricular inflow obstruction.[10 19 20]

From a small series such as this one cannot be dogmatic about the overall functional results of surgery. They do compare favourably, however, with the results of mitral repair for all congenital mitral anomalies reported by Carpentier and colleagues.[21] These authors found a persistent apical systolic murmur in 22 out of 34 patients, and a significant reduction in heart size in only seven.

Our present policy is therefore to perform two dimensional echocardiographic studies in all patients with clinical evidence of mitral regurgitation. If an isolated cleft is diagnosed and no other complicating suspected features are present, such as coarctation of

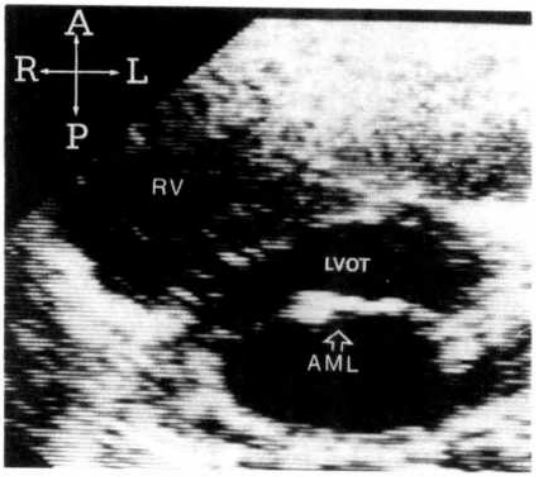

Fig. 7 *This is a postoperative short axis cut in a patient with a repaired localised cleft in the anterior mitral leaflet. Note the suture line indicated by the dense echo in the centre of the anterior mitral leaflet. See Fig. 2 and 3 for abbreviations.*

the aorta or severe pulmonary vascular disease, the degree of regurgitation is assessed clinically, radiographically, and by measuring left atrial and left ventricular sizes. If it is graded as moderate to severe, then the patients are submitted for surgical repair of the valve. Careful follow-up studies of mitral valve function in a large series of patients will obviously be necessary.

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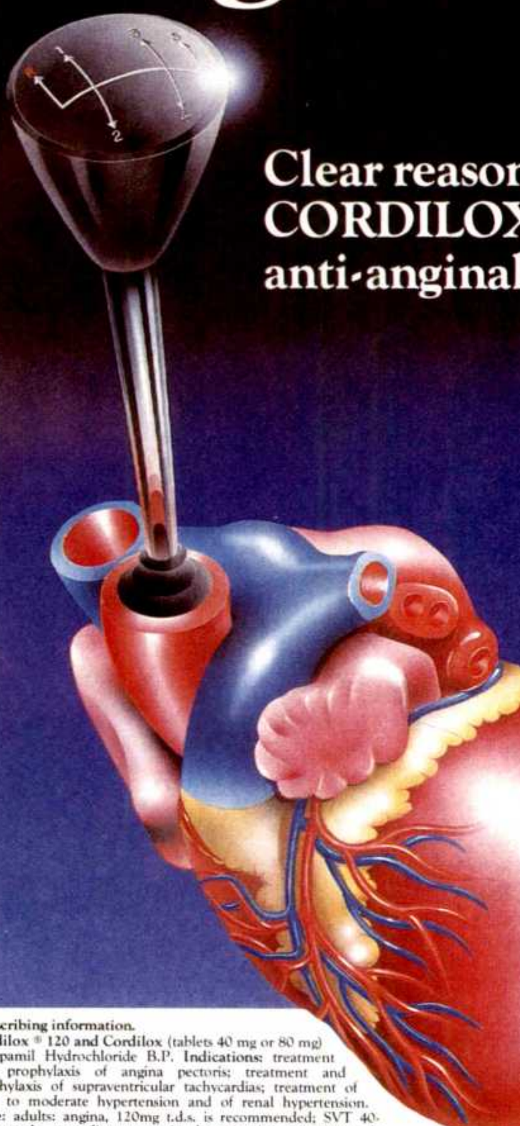

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essure. phenomena indicating a reduced blood supply to the heart may appear. PL/0424/0012. **Hospital Price:** £49.50 per 10 ampoules. Full prescribing
ormation is available from: Tillotts Laboratories. Henlow Trading Estate. Henlow. Beds.

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Cedocard. The comprehensive range of Isosorbide dinitrate.

Br Heart J 1982; **48:** 117–24

Mitral valve replacement in children

Comparative study of pre- and postoperative haemodynamics and left ventricular function

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SUMMARY Haemodynamic variables and left ventricular function were studied before and after mitral valve replacement in 44 children age 3 to 17 years (mean 11·9 years). Thirty-nine Starr-Edwards prostheses and five Hancock prostheses were used; postoperative study took place two to six months (mean 3·9 months) after operation. Pulmonary hypertension was present preoperatively in most patients, with mean pulmonary artery pressures of 18 to 75 (mean 46·5 mmHg). Postoperatively there was a pronounced drop in pressure to a mean value of 25·6 mmHg, partially explained by a decrease in pulmonary capillary wedge pressure. Pulmonary arteriolar resistance, however, also decreased conspicuously from an average of 590 dynes s cm^{-5} m^{-2} preoperatively to 282 dynes s cm^{-5} m^{-2} postoperatively. A return to normal resistance was seen in every case when preoperative resistance did not exceed 650 dynes s cm^{-5} m^{-2}; above this threshold some degree of pulmonary hypertension often persisted. The residual gradient across the prosthetic valve was slightly higher for the Hancock than for the Starr-Edwards prosthesis (mean 8·7 mmHg, vs mean 6·9 mmHg).

The left ventricular end-diastolic volume was much increased before surgery, with a mean value of 190 ml/m^2; it decreased conspicuously after operation to 103 ml/m^2. The left ventricular ejection fraction ranged from 40% to 76% (mean 57%) before operation; there was no significant change after operation, with values ranging from 40% to 73%.

This left ventricular dysfunction is probably the result of myocardial injury caused by a chronic volume overload and the sequelae of rheumatic carditis.

Mitral valve disease with regurgitation and stenosis gives rise to various haemodynamic consequences. First, there is left ventricular volume overload and dilatation of the left atrium and ventricle. Longstanding left ventricular volume overload may compromise left ventricular function.[1 2] If the mitral valve disease is of rheumatic origin, left ventricular function may also be depressed as a consequence of myocardial fibrosis, secondary to myocarditis. Secondly, pulmonary venous congestion will result in pulmonary hypertension; with time, pulmonary vascular disease may develop, compromising the return to normal pressures after mitral valve function is restored. Severe mitral valve disease often requires valve replacement, which is usually reserved for very disabled patients. Various degrees of left ventricular dysfunction and of pulmonary hypertension are usually therefore present, and the reversibility of such changes is uncertain. Haemodynamic assessment after mitral valve replacement is of use and has often been performed in adult patients,[3–5] but very few data are available in children.[6] We did not find any data concerning left ventricular function and volume after valve replacement in children.

We would like to report the results of postoperative catheterisation in 44 children who have undergone valve replacement for severe mitral valve disease, including the results of left ventricular volume studies in 30 children.

Patients and methods

Forty-four children (23 boys and 21 girls) with clinical and haemodynamic evidence of severe mitral valve

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disease were studied. The valve lesion was the result of rheumatic heart disease in 35, and of congenital malformation in nine. Their ages ranged from 3 to 17 years (mean 11·9 years). Twenty-nine patients had mitral regurgitation associated with mitral stenosis; 15 patients had pure mitral regurgitation. In 30 patients, there was significant disease of another valve: 12 had aortic regurgitation, 12 had tricuspid regurgitation, six had aortic and tricuspid regurgitation. Two had a ventricular septal defect. Thirty-three patients were in grade IV heart failure (according to the New York Heart Association), nine in grade III, and two in grade II. Thirty-nine underwent mitral valve replacement with a Starr-Edwards prosthesis and five with a Hancock prosthesis; nine patients also had a tricuspid annuloplasty (De Vega), and two aortic valve replacement (one Björk and one Starr-Edwards prosthesis). Two patients had closure of a ventricular septal defect.

These 44 patients are part of a group of 171 children who underwent valve replacement from 1969 to 1980 in Geneva.[7] Postoperative catheterisation was performed either to assess pulmonary pressure (when preoperative values were raised) or to rule out valve dysfunction in the presence of a systolic or diastolic murmur.

Cardiac catheterisation was performed two to six months (mean 3·9 months) after operation. The procedure was done under light sedation with a mixture of pethidine, promethazine, and chlorpromazine. Routine cardiac catheterisation was performed by percutaneous puncture of the right femoral artery and vein. Cardiac output was measured by the Fick method, with oxygen consumption assumed (table of La Farge and Miettinen). Pulmonary vascular resistance was calculated by the following formulae: TPVR=PA×80/CI; PAR=(PA–PAW)×80/CI, where TPVR is the total pulmonary vascular resistance in dynes s cm^{-5} m^{-2}, PAR is the pulmonary arteriolar resistance, PA and PAW are the mean pulmonary arterial and pulmonary arterial wedge pressures (mmHg), respectively, and CI is the cardiac index (litres/min per m^2).

Thirty patients underwent left ventricular cineangiography in the right anterior oblique projection using 1 to 1·5 ml/kg of 76% Urografin. Ventricular volumes were calculated using the Sandler and Dodge formula[8] from planimetered surfaces on the right anterior oblique cineangiogram. Ejection fraction (EF) was calculated with the following formula: EF%=(EDV–ESV)/EDV×100, where EDV and ESV are end-diastolic and end-systolic volumes, respectively. We took cardiac cycles early after opacification to obtain physiological information from cineangiocardiography.[9] The pre- and postextrasystolic systoles were excluded. Mean frequency systoles were taken when the patient was in atrial fibrillation. Absolute and indexed volume is reported in 27 patients only because the magnification factor was unknown in three.

Table *Haemodynamics and left ventricular function data*

Case No.	*Sex*	*Age*		*PA*	*PAW*	*MG*	*CI*	*TPVR*	*PAR*	*NYHA*	*RMR*	*Surgical treatment*	*LVED*	*EF*	*LVES*
1	F	15	Preop	45/24 $\overline{33}$	21	20	2·9	910	333	IV		Starr M	80	60	31
			Postop	35/18 $\overline{25}$	15	8	4·0	500	200	I-II	–	An. T	50	56	22
2	M	15	Preop	90/50 $\overline{68}$	30	—	2·5	2190	1220	IV		Starr M	—	—	—
			Postop	28/13 $\overline{20}$	7	8	4·9	330	212	I-II	–		—	—	—
3	M	13	Preop	40/20 $\overline{28}$	20	25	4·4	510	150	IV		Starr M	379	61	147
			Postop	28/11 $\overline{16}$	13	7	4·0	320	60	I	–		189	53	89
4	F	11	Preop	65/45 $\overline{55}$	30	—	1·9	2380	1050	IV		Starr M	—	—	—
			Postop	36/10 $\overline{17}$	6	5	3·6	350	240	II	–		—	—	—
5	F	13	Preop	42/13 $\overline{34}$	28	17	2·4	1130	200	IV		Starr M	176	62	67
			Postop	26/3 $\overline{16}$	8	7	4·1	310	160	I-II	–		109	50	56
6	M	7	Preop	30/10 $\overline{24}$	13	—	4·0	480	220	III		Hancock M	—	—	—
			Postop	25/13 $\overline{17}$	8	6	4·6	290	150	I-II	–		—	—	—
7	F	13	Preop	105/58 $\overline{75}$	45	44	1·9	3160	1260	IV		Starr M	337	65	120
			Postop	40/14 $\overline{26}$	5	2	4·0	520	420	I-II	–		119	65	42
8	F	16	Preop	58/29 $\overline{38}$	28	22	2·5	1220	920	IV		Starr M	95	64	34
			Postop	30/12 20	11	10	3·4	470	210	I-II	–		59	52	29
9	M	17	Preop	80/40 $\overline{60}$	29	24	2·7	1780	920	IV		Starr M	116	54	54
			Postop	75/40 $\overline{50}$	15	8	2·1	1900	1330	II	+		136	41	80
10	F	16	Preop	58/25 $\overline{40}$	30	—	2·2	1450	360	IV		Starr M	196	76	46
			Postop	25/14 $\overline{18}$	11	8	2·5	580	220	I-II	–		85	48	45
11	M	5	Preop	45/20 $\overline{30}$	15	—	2·7	890	440	IV		Starr M	—	—	—
			Postop	29/16 $\overline{18}$	7	?	3·7	390	190	I-II	–		—	—	—
12	F	10	Preop	38/28 $\overline{32}$	24	18	1·7	1510	380	IV		Starr M	94	49	48
			Postop	32/12 $\overline{24}$	15	6	3·2	600	225	I-II	–		92	44	52
13	M	5	Preop	50/35 $\overline{42}$	21	5	2·0	1680	840	IV		Starr M	—	59	—
			Postop	48/26 $\overline{35}$	16	10	2·8	1000	540	—	+	An. T	—	47	—
14	M	14	Preop	85/48 $\overline{59}$	30	10	2·1	2250	1100	IV		Starr M	197	55	89
			Postop	70/38 $\overline{50}$	19	10	2·3	1740	1080	—	+	An. T	183	50	91

Table (cont) *Haemodynamics and left ventricular function data*

Case No.	*Sex*	*Age*		*PA*	*PAW*	*MG*	*CI*	*TPVR*	*PAR*	*NYHA*	*RMR*	*Surgical treatment*	*LVED*	*EF*	*LVES*
15	M	17	Preop	65/25 $\overline{39}$	19	10	—	—	—	IV		Starr M	218	50	109
			Postop	28/12 $\overline{16}$	8	5	—	—	—	I-II	–	VSD clos.	—	47	—
16	M	10	Preop	82/35 $\overline{55}$	24	12	2·5	1760	990	IV		Starr M	159	58	67
			Postop	38/13 $\overline{23}$	14	8	3·6	510	200	I	–	An. T	114	74	30
17	F	11	Preop	46/26 $\overline{34}$	14	—	2·5	1090	640	IV		Starr M	118	58	50
			Postop	36/14 $\overline{25}$	13	8	3·8	530	253	I	–		87	62	33
18	F	12	Preop	26/12 $\overline{18}$	9	7	3·8	380	190	III		Starr M	—	—	—
			Postop	28/14 $\overline{17}$	11	?	4·8	280	100	I-II			—	—	—
19	M	13	Preop	90/56 $\overline{66}$	28	20	2·7	1960	1130	IV		Starr M	—	—	—
			Postop	24/8 $\overline{13}$	6	?	3·6	290	150	I	–		—	—	—
20	F	14	Preop	85/40 $\overline{60}$	28	—	2·0	2400	1280	IV		Starr M	—	—	—
			Postop	37/24 $\overline{27}$	9	8	3·8	570	380	I	–		—	—	—
21	M	15	Preop	84/42 $\overline{60}$	20	20	—	—	—	III		Starr M	—	—	—
			Postop	36/18 $\overline{25}$	11	8	—	—	—	I	–	VSD clos.	—	—	—
22	M	10	Preop	96/53 $\overline{72}$	16	—	3·9	1480	1150	IV		Starr M	—	—	—
			Postop	34/15 $\overline{24}$	12	?	4·5	430	210	II	–		—	—	—
23	F	—	Preop	28/12 $\overline{16}$	12	—	—	—	—	III		Starr M	—	—	—
			Postop	29/10 $\overline{18}$	13	?	—	—	—	II	–		—	—	—
24	F	7	Preop	90/50 $\overline{68}$	30	24	4·2	1300	720	IV		Starr M	292	52	134
			Postop	32/15 $\overline{20}$	6	3	5·9	270	190	I	–		80	56	35
25	M	11	Preop	37/16 $\overline{24}$	20	7	3·0	640	110	III		Starr M	361	68	115
			Postop	26/10 $\overline{14}$	9	7	3·4	330	120	I	–		60	70	19
26	F	11	Preop	45/20 $\overline{30}$	18	10	2·8	860	340	II		Starr M	181	68	58
			Postop	34/16 $\overline{20}$	12	6	4·2	380	150	I	–		87	66	30
27	M	15	Preop	75/35 $\overline{53}$	37	28	2·9	1460	440	IV		Hancock M	68	51	33
			Postop	54/19 $\overline{33}$	16	8·5	2·7	980	500	II	+		82	52	40
28	F	17	Preop	91/45 $\overline{61}$	47	40	1·5	3250	750	IV		Starr M	242	41	143
			Postop	50/22 $\overline{29}$	15	9	4·0	580	280	I-II	–	An. T	79	48	41
29	M	11	Preop	73/44 $\overline{58}$	31	23	2·7	1720	800	IV		Hancock M	—	76	—
			Postop	28/14 $\overline{18}$	14	13	5·3	270	60	I	–		—	53	—
30	F	6	Preop	61/33 $\overline{48}$	26	—	2·7	1420	650	III		Starr M	135	49	69
			Postop	32/15 $\overline{20}$	15	?	4·0	400	100	I	–		98	56	42
31	F	11	Preop	42/31 $\overline{36}$	—	—	2·3	1250	—	IV		Starr M	—	—	—
			Postop	37/15 $\overline{25}$	10	?	3·2	630	380	I-II	–		—	—	—
32	M	13	Preop	70/35 $\overline{50}$	27	18	2·7	1480	680	IV		Starr M	113	49	58
			Postop	44/15 $\overline{27}$	12	?	3·2	680	370	I-II	–		108	61	42
33	F	13	Preop	45/28 $\overline{36}$	23	8	3·3	870	320	III		Starr M	110	64	40
			Postop	24/10 $\overline{15}$	6	6	3·5	340	210	I-II	–		87	63	32
34	M	14	Preop	60/33 $\overline{48}$	30	10	2·5	1540	580	III		Starr M	257	55	117
			Postop	31/11 $\overline{18}$	9	6	3·4	420	210	I-II	–	Starr A	129	68	40
35	M	13	Preop	96/60 $\overline{73}$	32	30	3·0	1950	1090	IV		Starr M	171	62	65
			Postop	34/12 $\overline{23}$	5	4·5	3·6	510	400	I	–		55	57	23
36	M	10	Preop	80/45 $\overline{58}$	30	25	2·8	1660	800	IV		Starr M	255	45	140
			Postop	41/25 $\overline{31}$	14	7	3·5	710	390	II	+		250	47	133
37	M	3	Preop	55/29 $\overline{41}$	26	16	2·0	1640	600	IV		Starr M	—	—	—
			Postop	28/13 $\overline{20}$	12	5	4·0	400	160	I-II	–		—	—	—
38	M	16	Preop	57/38 $\overline{45}$	30	23	2·0	1800	600	IV		Hancock M	82	43	47
			Postop	37/17 $\overline{22}$	12	7	3·2	550	250	I-II	–	An. T	65	54	30
39	M	15	Preop	100/40 $\overline{60}$	24	—	2·6	1850	1110	IV		Starr M	—	—	—
			Postop	38/17 $\overline{27}$	12	8	4·4	490	270	I-II	–	An. T	—	—	—
40	F	13	Preop	110/40 $\overline{60}$	31	15	2·6	1850	890	IV		Starr M	188	64	68
			Postop	50/23 $\overline{33}$	16	10	4·7	560	290	II	–	An. T	63	73	17
41	M	10	Preop	46/23 $\overline{32}$	21	—	2·6	990	340	III		Hancock M	191	60	77
			Postop	37/18 $\overline{25}$	15	9	3·5	570	230	I	–		84	40	51
42	F	10	Preop	30/17 $\overline{22}$	11	—	3·6	480	240	II		Starr M	—	—	—
			Postop	29/13 $\overline{17}$	13	?	3·6	380	90	I	–	Björk A	—	—	—
43	F	13	Preop	77/22 $\overline{44}$	26	—	3·5	1010	410	IV		Starr M	241	54	109
			Postop	28/12 $\overline{19}$	13	5	5·0	300	100	I	–		114	55	51
44	F	11	Preop	48/20 $\overline{30}$	20	12	2·4	990	330	IV		Starr M	200	55	89
			Postop	28/10 $\overline{18}$	7	6	3·8	380	180	I	–		72	50	35
Mean			Preop	46·5	25·6	—	2·6	1340	590	—	–	—	190	57	—
Mean			Postop	23·4	10·9	—	3·8	533	282	—	–	—	103	56	—
p				<0·0001	<0·0001	—	<0·0001	<0·0001	<0·0001	—	–	—	<0·0001	>0·15	

A, aortic; An.T, tricuspid annuloplasty (De Vega); CI, cardiac index (l/min per m²); EF, ejection fraction (%); LVED, left ventricular end-diastolic volume (ml/m²); LVES, left ventricular end-systolic volume (ml/m²); M, mitral; MG, mitral gradient (mmHg); NYHA, New York Heart Association grade; PA, pulmonary artery pressure (mmHg); PAR, pulmonary arteriolar resistance (dynes s cm^{-5} m^{-2}); PAW, pulmonary arterial wedge pressure (mmHg); RMR, residual mitral regurgitation; TPVR, total pulmonary vascular resistance (dynes s cm^{-5} m^{-2}); VSD clos., ventricular septal defect closure.

Results

Complete data are shown in the Table.

PRESSURES

Pulmonary artery pressure was often much increased before operation, up to systemic level in some cases. The mean pulmonary artery pressure preoperatively ranged from 18 to 75, mean 46·5 mmHg. After operation, there was a pronounced decrease to values ranging from 10 to 42, mean 23·4 mmHg. This was highly significant ($p<0·0001$). In five patients, however, there was mitral regurgitation postoperatively, and pulmonary arterial pressure remained high (above 30 mmHg) (Fig. 1a).

Mean pulmonary arterial wedge pressure was high before operation (9 to 45, mean 25·6 mmHg); it decreased after operation (5 to 19, mean 10·6 mmHg) ($p<0·0001$). Five patients had pulmonary arterial wedge pressures higher than 15 mmHg after operation; each had mitral regurgitation caused by paravalvar leak (Fig. 1b).

CARDIAC INDEX

The cardiac index rose from an average of 2·6 litres/min per m^2 before operation, to 3·8 litres/min per m^2 ($p<0·0001$) after operation (lower limit of normal for our laboratory is 3·0 l/min per m^2). In patients with residual mitral regurgitation, cardiac index was lower than 3·5 litres/min per m^2 postoperatively (Fig. 2).

RESISTANCES

Total pulmonary vascular resistance was moderately or much raised before operation (450 to 3150, mean 1340 dynes s cm^{-5} m^{-2}), and it decreased after operation (250 to 970, mean 533) ($p<0·0001$).

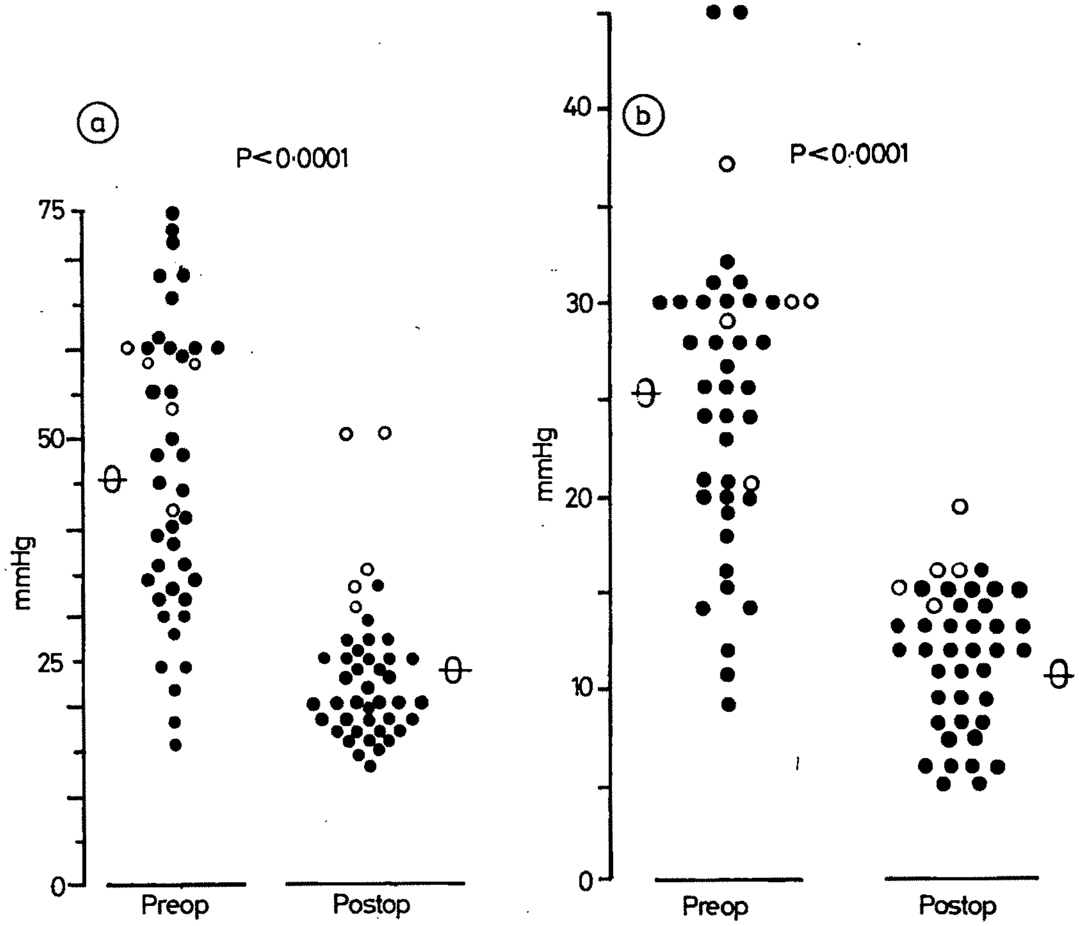

Fig. 1 *(a) Mean pulmonary artery pressure before and after mitral valve replacement. Open circles indicate patients with residual mitral regurgitation (paravalvar leak). (b) Mean pulmonary wedge pressure before and after mitral valve replacement. Open circles indicated patients with residual mitral regurgitation.*

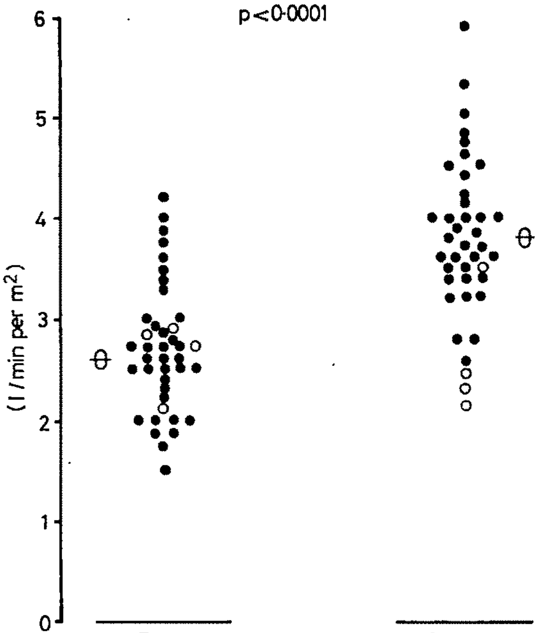

Fig. 2 *Cardiac index before and after mitral valve replacement. Open circles indicate patients with residual mitral regurgitation.*

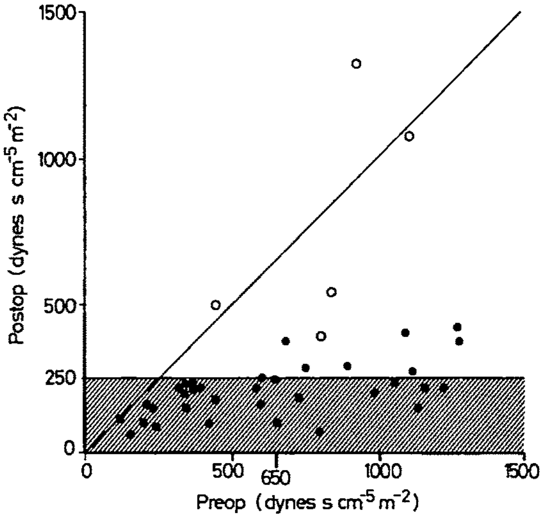

Fig. 3 *Postoperative pulmonary arteriolar resistance (on the y axis) plotted against preoperative resistance (on the x axis), with the line of identity. Shaded area indicates normal values. Open circles are patients with residual mitral regurgitation. In cases without residual regurgitation, resistances always return to normal when the preoperative value does not exceed 650 dynes s cm^{-5} m^{-2}.*

Pulmonary arteriolar resistance showed values between 120 and 1280, mean 590 dynes s cm^{-5} m^{-2} before operation; these values fell to 60 to 430, mean 282 dynes s cm^{-5} m^{-2} after operation ($p<0·0001$) (Fig. 3). In all patients with preoperative values lower than 650 dynes s cm^{-5} m^{-2}, postoperative resistance was found to be normal (≤250 dynes s cm^{-5} m^{-2}). If preoperative values exceeded 650 dynes s cm^{-5} m^{-2}, the pulmonary arteriolar resistance decreased, but a return to normal was not the rule. Patients with residual regurgitation had pulmonary arteriolar resistance above 500 dynes s cm^{-5} m^{-2}, unchanged from preoperative values (Fig. 3).

RESIDUAL MITRAL GRADIENT

A residual mitral gradient was commonly found after valve replacement in children. This was mild for the Starr-Edwards prostheses, with a gradient ranging from 2 to 10, mean 6·9 mmHg. For the Hancock prostheses, the gradient was somewhat higher, between 6 and 13, mean 8·7 mmHg (not significant). Though the difference between means is not statistically significant, it appears that one third of the patients with Starr-Edwards prostheses have insignificant gradients, between 2 and 6 mmHg; no child with a Hancock prosthesis had such a small gradient.

VENTRICULAR VOLUMES

End-diastolic left ventricular volumes were raised before operation (83 to 379, mean 190 ml/m²). Seventeen patients had left ventricular end-diastolic volumes higher than 150 ml/m², five patients had values between 110 and 150 ml/m², but five had values lower than 100 ml/m². Left ventricular end-diastolic volumes decreased after valve replacement and showed values between 55 and 250, mean 103 ml/m² ($p<0·0001$) (Fig. 4). In 16 patients, the ventricular volume fell below 100 ml/m², and six had values between 100 and 130 ml/m². Five still had values above 130 ml/m². Among these there was a case of moderate aortic regurgitation, who needed aortic valve replacement later; in three other patients, high postoperative left ventricular volume was related to residual mitral regurgitation.

EJECTION FRACTION

Left ventricular ejection fraction was measured before and after operation (Fig. 5). Before operation, about half of the patients had a depressed ejection fraction; the values ranged from 40 to 76%, mean 57%. Thirteen patients had values higher than 60%, 10 patients had values between 50 and 60%, and seven patients had values lower than 50%. After operation, these values did not change significantly; they were

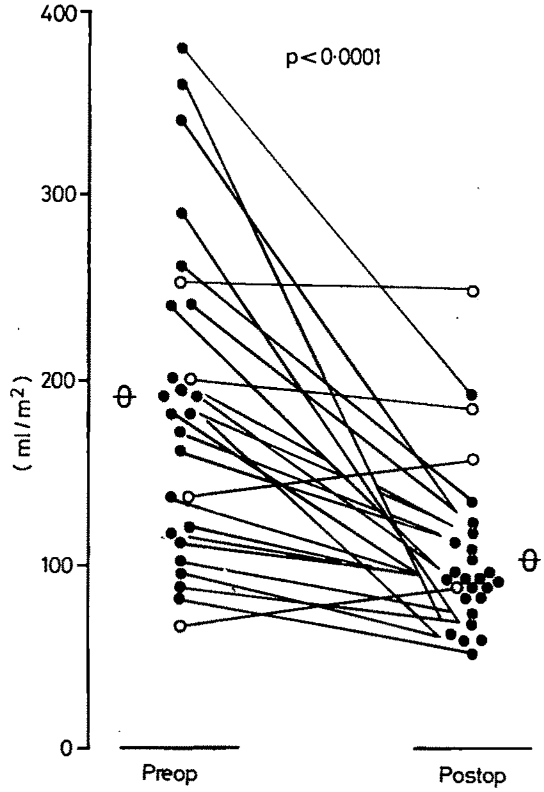

Fig. 4 *Left ventricular end-diastolic volume (LVED) before and after mitral valve replacement. LVED decreased significantly after valve replacement in patients without residual mitral regurgitation. Open circles indicate patients with residual mitral regurgitation.*

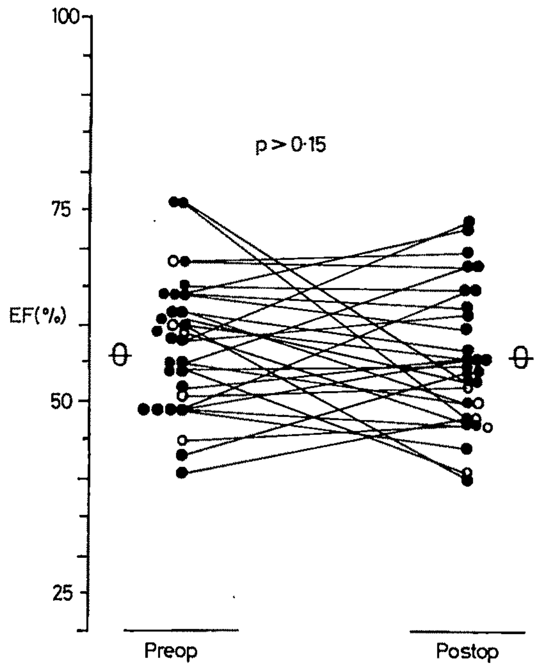

Fig. 5 *Left ventricular ejection fraction (EF) measured before and after operation. The values are often below normal before as well as after operation, and there is no significant difference between preoperative and postoperative values.*

situated between 40 and 73%, mean 56%. No relation was found between the ejection fraction and age of the patient.

Discussion

Mitral valve replacement in children is usually restricted to patients who are severely symptomatic and in whom mitral valve repair is not feasible. The short term results are satisfactory and the children are much improved.[7] Since valve replacement, however, is usually performed after a long period of progressive heart failure, complications are often present: longstanding left ventricular overload, together with sequelae of myocarditis in the case of rheumatic heart disease, may result in left ventricular dysfunction; on the other hand, chronically increased left atrial pressure will result in pulmonary hypertension. It is therefore interesting to assess postoperative haemodynamics and left ventricular function after valve replacement and to compare the results with preoperative data.

HAEMODYNAMIC VARIABLES

Even extreme degrees of pulmonary hypertension and increased pulmonary vascular resistance secondary to mitral valve disease regress conspicuously in adult patients[3 4] and children[6] who underwent adequate valve replacement, though a return to normal is not the rule. Thus, severe pulmonary hypertension is no longer a contraindication for operation, as had been suggested previously by some.[10] This regression is partially the result of left atrial decompression: the pronounced reduction in left atrial pressure (pulmonary wedge pressure) explains the impressive reduction in total pulmonary vascular resistance. As shown in the present study, however, pulmonary arteriolar resistance, which is not directly related to left atrial pressure, also decreases conspicuously. The degree of increase in pulmonary arteriolar resistance before operation seems to be a determinant of residual postoperative pulmonary hypertension. Indeed, when preoperative values were below 650 dynes s cm^{-5} m^{-2}, a return to normal resistance was always observed. Above this level, some degree of pulmonary hypertension often persisted. In four of our seven patients with increased pulmonary arteriolar resistance after operation and no mitral regurgitation, the residual mitral gradient was somewhat above the average. In no case, however, did it exceed 10 mmHg and we do not believe that this alone would explain the increased pulmonary arteriolar resistance. As the postoperative catheterisation took place fairly soon after operation, we do not know whether a further decrease may occur later in these cases. It is obvious, however, that the high resistances measured before operation are not the result of advanced pulmonary vascular disease, but rather of pulmonary arteriolar spasm. The situation is obviously different from pulmonary hypertension secondary to left to right shunt; indeed, pulmonary arteriolar resistance, measured two to four months after closure of a ventricular septal defect with pulmonary hypertension, does not change from preoperative values (B Friedli, unpublished data).

We have noted a significant increase in cardiac output after operation from the usually low preoperative values. It also appeared that some degree of residual mitral gradient may be found in children after mitral valve replacement: in our series, this was somewhat more significant for the Hancock porcine xenograft than for the Starr-Edwards prostheses. This is because for the same prosthetic valve diameter, the valve orifice is smaller in the Hancock prosthesis than in the Starr-Edwards prosthesis. As the postoperative study was done early, calcification of the porcine xenograft[11] could not at that stage have been responsible for the relative stenosis.

Mitral regurgitation (paravalvar leak) was found in five patients. This relatively large number can be explained by the fact that the 44 patients catheterised in this study were selected from 171 children who had received valve prostheses during that period. Indications for recatheterisation were the presence of a residual murmur or preoperative pulmonary hypertension. It is obvious from the present study that, when significant residual mitral regurgitation is present, the haemodynamic variables remain abnormal, similar to the levels before operation.

LEFT VENTRICULAR VOLUME AND FUNCTION

To our knowledge, these variables have not been previously studied in children with valve prostheses. Left ventricular volume is considerably increased before operation, because of chronic left ventricular volume overload. Similar increases have previously been found experimentally[12] as well as in adult patients.[13] After operation, there is a pronounced decrease in volume, but a return to normal is not the rule: the mean left ventricular volume remains raised around 100 ml/m². Left ventricular ejection fractions before operation vary over a wide range, but they are quite often abnormally low. There was no significant change in the mean, after operation, though some individual values did either increase or decrease. It must be emphasised that ejection fractions before and after mitral valve replacement cannot be directly compared because of the different haemodynamic setting. Indeed a series of variables, which determine left ventricular stroke volume, also influence ejection fraction. They are preload (left ventricular end-diastolic volume), afterload (left ventricular wall stress during ejection), myocardial contractility, and heart rate. In mitral regurgitation, preload is increased and afterload decreased. This should enhance ejection fraction; it has been shown that the "unloading" of the left ventricle in mitral regurgitation may mask the effect of depressed myocardial contractility on overall pump function.[14] This indicates that, in some of our patients, quite severe left ventricular dysfunction must have existed before operation, as the ejection fraction remains low in spite of the decreased afterload. One would also expect that ejection fraction decreases after mitral valve replacement, because of the increased afterload and decreased preload. This has been shown to occur in adults,[15 16] but we did not find it in the present study. One explanation for this difference may be because left ventricular volume decreases considerably in children after valve replacement, more so than in adults. The reduction in left ventricular dimension (radius) reduces left ventricular stress, that is afterload. Thus, afterload increase after valve surgery in children may be less important than in adults.

As to the cause of the left ventricular dysfunction, before as well as after operation, two factors need to be considered: chronic volume overload may itself produce myocardial changes that are not completely reversible, as shown in the electron-microscopical studies of Papadimitriou *et al.*[17] After closure of a ventricular septal defect—another cause of chronic left ventricular volume overload in children—Jarmakani *et al.*[1] showed some left ventricular dysfunction, except in those patients who were operated on very early, before two years of life. In the present study, we have not been able to show a clear effect of age or duration of disease on left ventricular ejection fraction. There is obviously another possible cause of myocardial dysfunction in patients with rheumatic heart disease, that is myocardial fibrosis secondary to rheumatic myocarditis. Indeed, many children in this study have had repeated attacks of rheumatic fever.

The indication for valve replacement in children remains, as mentioned previously, the presence of severe, often longstanding heart failure. This is because of the complications of valve prostheses which occur in children,[18] [19] as well as in adults.[20] The price of this conservative approach may be the presence of irreversible myocardial damage at the time of operation. In adults the results of valve replacement in grade IV heart failure are not as good as those in grade III heart failure.[21] Should a new valve prosthesis with low thromboembolic risk and long durability be developed, valve replacement at an earlier stage, for example in grade II, would therefore be indicated.

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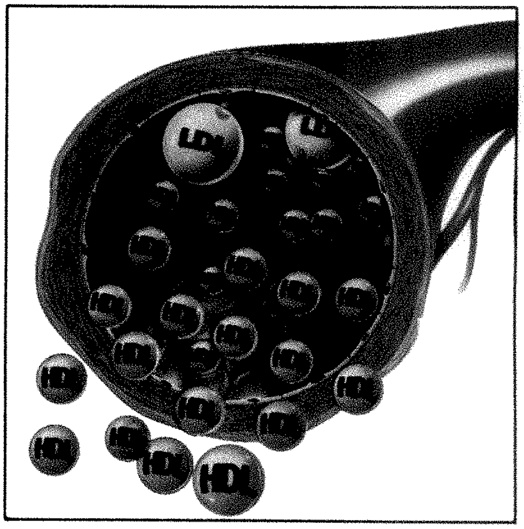

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Creatinine Clearance (ml/min 1.73 m^2)	Dosage Interval (Hours)
>75	8
75-35	12-24
34-20	24-48
19-8	48-72
7-5	72-108 (3 to 4.5 days)

When concomitant diuretic therapy is required, a loop diuretic (e.g. frusemide) is preferable to a thiazide diuretic.

Children Safety and effectiveness in children have not been established. Starting dose should be 1 mg per Kg bodyweight up to a maximum of 6 mg per Kg bodyweight divided into three doses per day. **CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS:- Contra-Indications** Previous hypersensitivity to Capoten **Warnings** NEUTROPENIA/ AGRANULOCYTOSIS and PROTEINURIA have been reported in patients receiving Capoten. Urinary protein should be checked (dip stick) prior to treatment, monthly for 8 months and periodically thereafter. WBC should be carried out prior to treatment, fortnightly for three months and periodically thereafter. **Hypotension** A precipitous reduction of blood pressure may occasionally occur within the first three hours following the initial dose of Capoten in patients on diuretics, on a low sodium diet or undergoing dialysis. An exaggerated hypotensive effect may also occur with one or two subsequent doses. Medical supervision should be maintained for one hour after the initial dose. This transient hypotensive response is not a contra-indication to further doses which can be given without difficulty once blood pressure has increased after volume expansion. **Hypotension in Patients with Severe Congestive Heart Failure.** These patients, having either normal or low blood pressure, may experience marked falls in blood pressure, which have on rare instances been associated with arrhythmia or conduction defects, after the first few doses of Capoten. Because of the potential fall in blood pressure in these patients, therapy must be started in the hospital. Patients should be followed closely for the first two weeks of treatment and whenever the dose of Capoten and/or diuretic is increased. Patients treated for severe congestive heart failure should be warned to increase their physical activity slowly. **Serum Potassium** Since Capoten decreases aldosterone production, elevation of serum potassium may occur, especially in patients with renal failure. Potassium sparing diuretics or potassium supplements, if needed, should be used with caution, since they may lead to a significant increase in serum potassium. **Changes in Renal Function** Some patients with renal disease, particularly those with renal artery stenosis, have developed increased serum concentration of BUN and serum creatinine after reduction of blood pressure with Capoten, usually along with a diuretic. Capoten dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalise blood pressure and maintain adequate renal perfusion. **Pregnancy** The safety of Capoten in pregnancy has not been established. **Nursing Mothers** Exercise caution. **Surgery/ Anaesthesia** In patients undergoing major surgery, or during anaesthesia with agents which produce hypotension, Capoten will block angiotensin II formation secondary to compensatory renin release. This may lead to hypotension which can be corrected by volume expansion. Capoten may cause a false-positive urine test for acetone. **Side Effects** Neutropenia/ Agranulocytosis Proteinuria see Warnings. Skin rashes and taste disturbance have been reported. Gastric irritation and abdominal pain may occur. **Other** Paraesthesias of the hands, serum sickness, cough, bronchospasm and lymphadenopathy have been reported. Hypotension - see Warnings. Tachycardia has been observed in a few volume depleted patients. **Overdosage** In the event of overdosage, hypotension would be the most important problem. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoring the blood pressure to normal. Capoten is removed by dialysis. **PACKAGE QUANTITIES** in bottles of 100. **Basic NHS Price** 25 mg tablets 100 - £21.40. **PRODUCT LICENCE NUMBERS, NAMES AND ADDRESSES Product Licence Numbers** Capoten tablets 25 mg PL 0034/0193;
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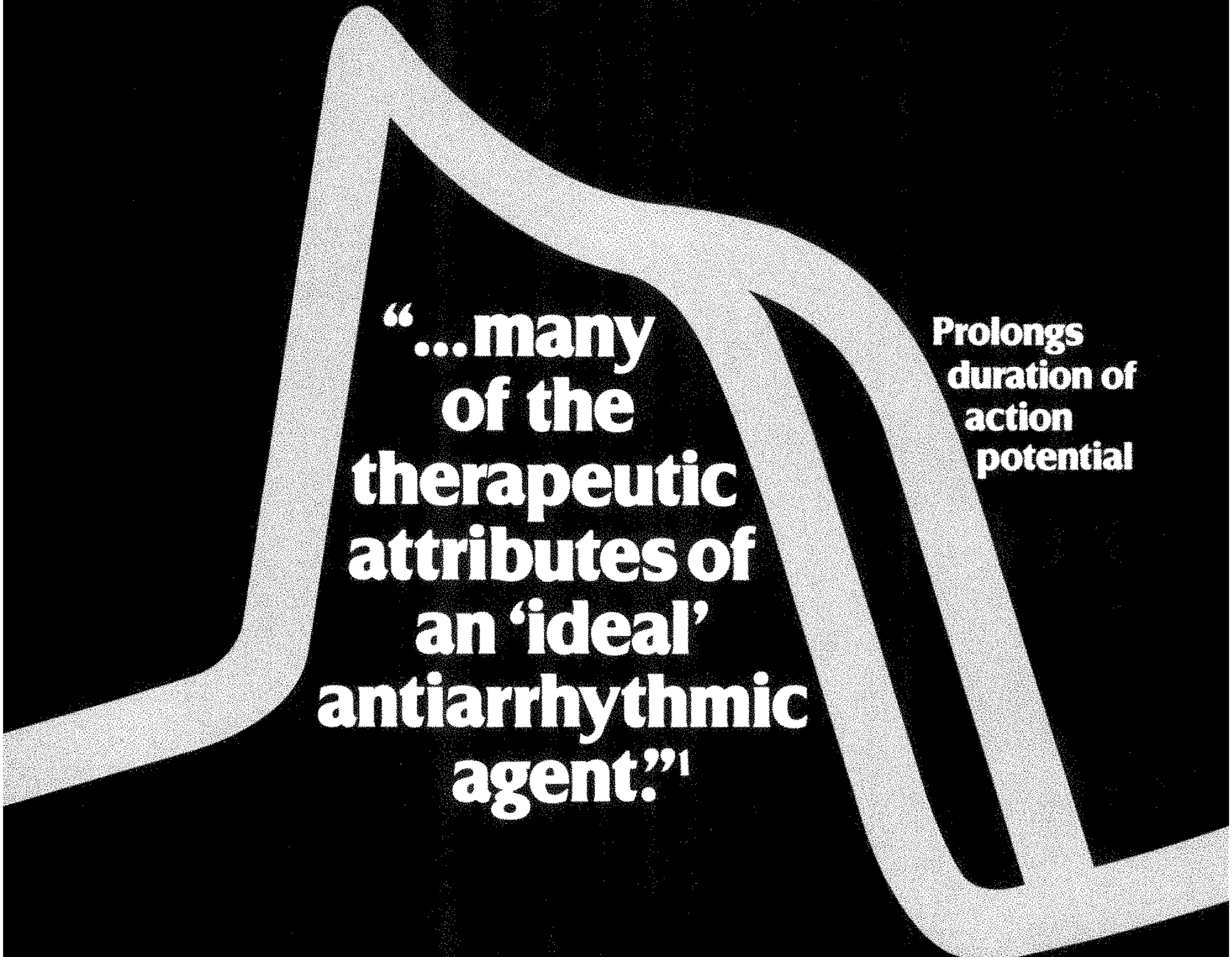

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Br Heart J 1982; **48**: 125–9

Independence of changes in left ventricular diastolic properties of pericardial pressure

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From the Brompton Hospital, London

SUMMARY There has been much interest in the published reports as to the extent to which measured left ventricular diastolic properties are affected by the pericardium. In this study observations were made on 24 patients, seven days after cardiopulmonary bypass. Left ventricular dimensions were measured from echocardiographic recordings and left ventricular diastolic pressure assessed from measurements of isovolumic relaxation time. Pericardial pressure was measured directly using a small solid state transducer inserted into the pericardial space at the time of operation. Left ventricular diastolic properties were altered by either isometric handgrip or glyceryl trinitrate administration. Isometric handgrip produced an increase in cavity dimension at end-systole and diastole, with reduction in isovolumic relaxation time, suggesting an increase in left ventricular end-diastolic pressure; glyceryl trinitrate produced the reverse effect, with decreased cavity dimensions and prolongation of isovolumic relaxation time. These changes occurred in the absence of significant changes in pericardial pressure. We therefore conclude that even in the rather unusual conditions of the early postoperative period, when the sensitivity of pericardial pressure to small volume changes might be expected to be increased, substantial changes in left ventricular diastolic properties can occur without detectable alteration in pericardial pressure.

There has been considerable interest concerning the extent to which the pericardium affects measured left ventricular diastolic properties. To date, most observations on this relation have been made on experimental animals and there have been few recorded measurements in man. We have taken advantage of the development of a small solid state transducer (Gaeltec 3EA) to measure pericardial pressure directly in man in the postoperative period after cardiopulmonary bypass. Left ventricular diastolic properties have been altered using isometric stress testing and glyceryl trinitrate administration and associated changes in pericardial pressure measured.

Subjects and methods

Twenty-four patients were studied during the postoperative period after cardiopulmonary bypass for saphenous vein bypass grafting in 18 patients, and for valve replacement in six.

Pericardial pressure was measured with a Gaeltec 3EA solid state transducer. This had an external diameter of 3 mm, low temperature sensitivity, and a resonant frequency of 50 kHz. The zero drift was low and in the present study was found to be < 2 mmHg in 10 days. It was calibrated in saline at 37°C before insertion and was used in conjunction with a Gaeltec S7 control unit amplifier with an isolated input.

The transducer was inserted into the pericardial space by a separate wound at the end of the operation and was left in situ for up to 10 days. The pericardium was closed once the transducer had been positioned. Previous studies[1] had shown that the site used for transducer placement did not significantly affect the pressure recorded. In all cases the zero for pressure measurement was taken as atmospheric.

Daily recordings of mean and phasic pericardial pressure were recorded. On the seventh postoperative day, simultaneous echo-, phono-, and apexcardiographic recordings were also made along with standard lead II of the electrocardiogram using Cambridge Instruments Equipment. Echocardiograms were recorded at the level of the tips of the mitral valve leaflets to show the time of separation of anterior and posterior cusps at the start of ventricular filling. Left ventricular cavity size was estimated at this level as the distance between the leading edge of the echoes from the left side of the septum and the endocardium

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of the posterior wall. Phonocardiograms were recorded from the left sternal edge, using a medium or high frequency filter in the position where A_2, the onset of the initial high frequency vibration of the aortic component of the second heart sound, was most obvious. This was definitively identified either from its relation to the dicrotic notch of the indirect carotid pulse, or from the aortic valve echogram. Apexcardiograms were recorded using a transducer of time constant 4 seconds and lower frequency limit of 0·05 Hz. Records were made photographically at a paper speed of 100 mm/s and digitised.[2]

From these records, the following measurements were made.

(1) DIMENSIONS
From the digitised echocardiogram—end-diastolic (synchronous with the q wave of the electrocardiogram) and minimum cavity dimension.

(2) TIME INTERVALS
(a) Isovolumic relaxation time—the interval between A_2 and the onset of mitral valve opening. This interval has previously been shown to bear strong and negative correlation with left ventricular end-diastolic pressure.[3]
(b) A_2 to the O point of the apexcardiogram. This interval has been studied in the past as isovolumic relaxation time[4] but can be more usefully regarded as a measure of the time taken by the left ventricular pressure to fall to its minimum value at the end of ejection. Like true isovolumic relaxation time ((a) above) this interval is strongly and negatively correlated with left ventricular end-diastolic pressure.[3]
(c) O point to the peak of the f wave (rapid filling wave in early diastole) of the apexcardiogram.

(3) RELATIVE AMPLITUDE OF F WAVE OF APEXCARDIOGRAM EXPRESSED AS PERCENTAGE OF TOTAL AMPLITUDE
The timing and relative amplitude of the f wave relate to both the duration of the isovolumic relaxation time and the end-diastolic pressure, a high end-diastolic pressure being associated with an earlier f wave of increased relative amplitude.[3]

After completing control measurements, the patients performed isometric handgrip by squeezing a sphygmomanometer bulb at 30% of the maximum force they could generate for three to five minutes until the onset of fatigue. Recordings of pericardial pressure and echo-, phono-, and apexcardiograms were made during the last 30 seconds of effort. After 20 minutes rest, control measurements were repeated and the patients took two 0·5 mg glyceryl trinitrate tablets sublingually over an interval of five minutes. Measurements of pericardial pressure and echo-, phono-, and apexcardiographic recordings were repeated at two, five, 10, and 20 minutes; those coinciding with the maximum heart rate response were noted. Changes in measured diastolic properties were correlated with changes in pericardial pressure.

This study had the approval of the Ethics Committee of the National Heart and Chest Hospitals.

Results

(1) PERICARDIAL PRESSURE MEASUREMENTS—MEAN AND PHASIC
During the first 24 hours after operation, the mean pericardial pressure was in the range of 2 to 5 mmHg. After this time there was a consistent fall in mean pressure to less than 3 mmHg, the average value by the seventh postoperative day being 2±1 mmHg (mean ± 1 SD) (Fig. 1). Phasic waveforms varied with mean pericardial pressure, so that when pressure was low, the overall amplitude of the waveform was small. Regardless of amplitude, however, the highest values in the cardiac cycle were always recorded during isovolumic contraction, reaching a peak which coincided with ejection. Pericardial pressure then fell and was at its lowest during late ejection or isovolumic relaxation, increasing again during ventricular filling (Fig. 2).

In individual patients, measurements of pericardial pressure were closely linked to clinical status, for example high pericardial pressures were found to correlate with the presence of postoperative tamponade.

(2) EFFECTS OF GLYCERYL TRINITRATE AND ISOMETRIC EXERCISE

(a) *Heart rate, arterial pressure, and cavity dimensions*
Well documented changes[3] in heart rate and arterial pressure were produced by glyceryl trinitrate administration and isometric exercise. Glyceryl trinitrate produced an increase in heart rate (mean increase: + 5 beats/min) and decrease in systolic (− 11 mmHg) and diastolic (− 3 mmHg) arterial pressure. Isometric exercise caused an increase in both heart rate (+ 15 beats/min) and systolic (+ 28 mmHg) and diastolic (+ 15 mmHg) pressure.

After administration of glyceryl trinitrate cavity dimensions fell at end-systole (mean decrease = 0·9 mm, $p<0·001$) and end-diastole (mean decrease = 2·9 mm, $p<0·001$) (Table 1). Isometric stress caused an increase in cavity dimension at end-systole (+ 1·0 mm, $p<0·001$) and end-diastole (+ 1·8 mm, $p<0·001$) (Table 1).

(b) *Diastolic time intervals* (Table 2)
Glyceryl trinitrate prolonged isovolumic relaxation time from 82±6 ms to 112±8 ms ($p<0·01$), A_2-O point

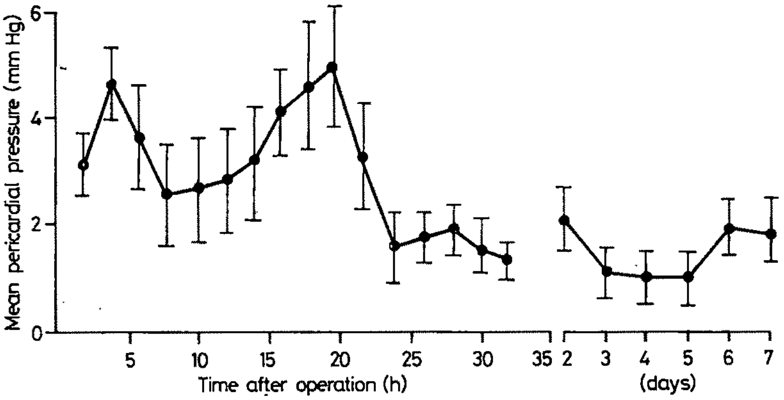

Fig. 1 *Mean pericardial pressure at varying time intervals after cardiopulmonary bypass. Results shown are mean ± 1 SD.*

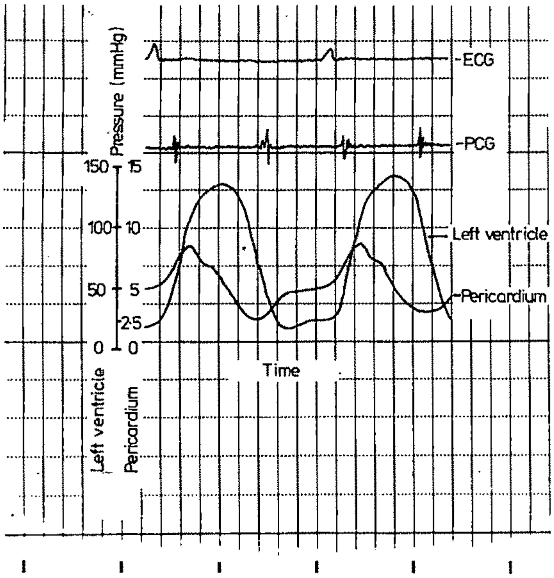

Fig. 2 *Phasic waveform of pericardial pressure with superimposed left ventricular pressure trace.*

interval from 138±18 ms to 153±10 ms ($p<0{\cdot}05$), and O-f wave interval from 76±8 ms to 85±3 ms ($p<0{\cdot}05$); the relative amplitude of the f wave fell from 24±9 to 11±6% ($p<0{\cdot}02$). Isometric stress caused isovolumic relaxation time to shorten from 86±8 ms to 69±5 ms ($p<0{\cdot}01$); A_2-O point and O-f intervals tended to shorten but these changes did not reach statistical significance.

(c) *Pericardial pressure*

Under control conditions, mean pericardial pressure on the seventh postoperative day was 2±1 mmHg (Fig. 1). After glyceryl trinitrate administration or isometric stress testing, there were no significant changes in pressure recorded, values being 1±1 and 2±1 mmHg, respectively (Table 2). The amplitude of phasic changes in pericardial pressure was not affected.

Discussion

Left ventricular diastolic pressures have considerable physiological significance and are frequently used to document the presence of disease or as a basis for clinical decision making. Their rigorous determination, however, presents difficulties, since the zero reference is usually taken as the pressure at mid-thorax, sternal angle, or of the atmosphere, so that pressure differences across the myocardium are not, in fact, measured. Whether this technical limitation is of clinical or physiological significance remains uncertain, though when contradictory findings arise in the course of experiment, the fundamentals on which such measurements are based must be carefully examined. For this reason we have determined pericardial pressure directly in patients after open heart surgery. The method, described in detail elsewhere,[1] involves the positioning of a solid state transducer immediately behind the posterior left ventricular wall, its exact position being unimportant. Mean and phasic traces derived by this method are similar to those previously reported from animals,[5-7] and in individual patients they have been found to correlate with the presence or absence of postoperative tamponade. In the present study, measurements were made seven days after operation. A possible limitation of the method is that it is applicable only to patients who have undergone open heart surgery, and who are

Table 1 *Effect of isometric handgrip and glyceryl trinitrate administration on cavity dimensions at end-systole (ESD) and end-diastole (EDD)*

Case No.	*Isometric exercise*				*Glyceryl trinitrate*			
	EDD (mm)		*ESD (mm)*		*EDD (mm)*		*ESD (mm)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	58	60	46	47	59	56	46	46
2	51	52	40	42	51	50	40	39
3	40	41	33	35	39	37	32	31
4	43	44	31	32	43	40	30	30
5	43	43	32	33	44	40	32	30
6	42	43	31	32	42	40	29	27
7	41	44	33	33	41	39	32	32
8	48	49	35	36	47	42	35	35
9	38	42	28	30	38	34	27	26
10	39	42	31	32	39	37	30	30
11	38	41	31	31	38	35	31	30
12	34	36	26	27	33	30	24	22
13	41	42	28	29	40	38	28	28
14	46	47	32	33	46	41	33	31
15	50	52	39	39	50	46	40	40
16	48	50	40	42	48	45	38	36
17	39	39	32	33	39	36	30	30
18	50	51	37	38	51	47	38	37
19	43	45	30	32	43	42	31	30
20	41	43	32	33	41	39	32	31
21	40	42	32	32	40	39	31	30
22	46	49	36	38	47	42	36	34
23	46	48	36	37	46	43	37	36
24	40	44	31	31	39	37	30	30
Mean increase	1·83 mm		1·04 mm					
Mean decrease					2·88 mm		0·90 mm	
Significance	$p<0.001$		$p<0.001$		$p<0.001$		$p<0.001$	

Table 2 *Effect of isometric handgrip and glyceryl trinitrate administration on isovolumic relaxation time and on pericardial pressure*

		Control	*Change*
Glyceryl trinitrate	Isovolumic relaxation time (ms)	82 ± 6	+ 30 ± 5 ($p<0.01$)
	Pericardial pressure (mmHg)	2 ± 1	− 1 ± 1 (NS)
Isometric handgrip	Isovolumic relaxation time (ms)	86 ± 8	− 17 ± 7 ($p<0.01$)
	Pericardial pressure (mmHg)	2 ± 1	0 ± 1 (NS)

thus more likely than normal subjects to have left ventricular disease. In addition, the pericardium, having recently been subject to surgical trauma, is likely to be oedematous and hyperaemic, so that it is likely to be stiffer than normal, and the complicance of the pericardial space reduced.

In spite of these considerations, pericardial pressure seven days after operation was low, and was unaffected by changes in left ventricular cavity size induced by glyceryl trinitrate or isometric handgrip. These latter were large, amounting to approximately 10% of transverse dimension, which might be expected to correspond to volume changes between 25 and 30%. Since glyceryl trinitrate is normally held to act by reducing venous return, right ventricular cavity size is also likely to have fallen. Similarly, after isometric handgrip, left atrial and hence pulmonary artery pressure can both be presumed to have risen, so that right ventricular volume changes were in the same direction as those of the left. We conclude, therefore, that even in the rather unusual conditions of the early postoperative period when the sensitivity of pericardial pressure to small volume changes might be expected to be increased, substantial changes in cardiac chamber size can occur without detectable alteration in pericardial pressure.

In spite of this, however, changes in left ventricular diastolic pressure could be shown. Glyceryl trinitrate caused arterial pressure to fall and yet isovolumic relaxation time was prolonged, suggesting a significant fall in left atrial and left ventricular end-diastolic pressure,[3] while exactly the reverse occurred during isometric handgrip. Thus, these two manoeuvres both caused well defined changes in left ventricular diastolic behaviour, suggesting significant changes in both end-diastolic pressure and volume.

There has been much interest in the published reports as to the extent to which measured left ventricular diastolic properties are affected by the pericardium. Holt's early work[8] suggested an effect of the pericardium on the diastolic pressure-volume relations of the ventricle, which were significantly shifted when the pericardium was removed. Similarly, volume loading of the heart with the pericardium intact in dogs shifts the entire left ventricular pressure volume curve upwards, primarily because of a rise in intrapericardial pressure.[9] Nitroprusside infusion in the presence of such acute cardiac distension displaces the curve downwards again as pericardial pressure falls. These acute shifts are abolished after removal of the pericardium. By contrast, Mann *et al.*[10] noted that when patients with ischaemic heart disease were paced, the increase in left ventricular end-diastolic pressure in the left ventricle was greater than that in the right. This finding is incompatible with the idea that the increase in left ventricular end-diastolic pressure is solely the result of mechanical coupling between the two ventricles, mediated by an intact pericardium. Similarly, Ludbrook *et al.*[11] noted that administration of glyceryl trinitrate shifted the pressure-volume curve downwards in a group of patients with ischaemic heart disease. Since right ventricular pressures and left ventricular end-diastolic volumes were not significantly increased in any of their patients, it seems unlikely that pericardial restriction played any significant part in the displacement of the pressure-volume curves. Our results are wholly compatible with these. Major changes in left ventricular cavity size, and probably in left ventricular end-diastolic pressure occurred in the absence of any significant change in pericardial pressure. Clearly, these observations do not exclude such an increase in individual cases as a mechanism of impairment of left ventricular filling; indeed, it forms the basis of the haemodynamic disturbance of pericardial tamponade. It is uncommon, however, closely related to the presence of pericardial disease, and does not appear to operate in the majority of cases. We conclude, therefore, that changes in left ventricular diastolic function measured invasively by others, and non-invasively by ourselves cannot be routinely ascribed to such external influences. Rather, it seems that primary changes in the passive properties of the left ventricle can be induced by drugs or other manoeuvres in patients with heart disease. The exact nature of these changes remains obscure, though their clinical and theoretical significance is profound. With their existence more firmly established, further studies of their underlying mechanism seem justified.

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Exercise testing in mitral valve prolapse before and after beta blockade

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SUMMARY Exercise electrocardiograms must be interpreted with the understanding that not every positive test is indicative of coronary artery disease. Mitral valve prolapse mimics coronary heart disease clinically and often in the electrocardiographic response to exercise. Twelve patients with mitral valve prolapse in whom exercise testing was positive underwent a repeat study after beta blockade. All tracings returned to normal after adequate blockade, evidenced by 17 to 22% reduction of resting and exercise heart rates. To the best of our knowledge, this is the first such report in the English literature.

The results of this study suggest that an exercise test after beta blockade should become part of the routine procedure in such patients. The elimination of false positive electrocardiographic responses by beta blockade should help improve the specificity of the exercise test. Moreover, similar responses should lead to the suspicion of mitral valve prolapse.

The resting electrocardiogram is a poor predictor of coronary disease, and the value of exercise testing in detecting myocardial ischaemia remains controversial.[1] Exercise tests must be interpreted with the understanding that not every positive test is indicative of coronary artery disease.

Mitral valve prolapse is a common entity, many of whose features mimic those of coronary artery disease. Resting and exercise-induced electrocardiographic abnormalities in repolarisation in patients with mitral valve prolapse compound further the problem of differentiation.

One of us has studied the effect of beta blockade on the resting electrocardiogram in mitral valve prolapse[2] and suggested that these changes may be due to the result of sympathetic overactivity. As exercise testing in mitral valve prolapse often induces changes in repolarisation, which mimic coronary heart disease, it seemed appropriate to investigate the effect of beta blockade on the electrocardiographic response to exercise in these patients.

Subjects and methods

Thirty-eight patients with mitral valve prolapse underwent exercise testing. Twelve (31·6%) of these patients, nine women and three men, had a positive test. Their average age was 42, with a range of 24 to 55 years. All patients had clinical and echocardiographic evidence of mitral valve prolapse. Those revealing pathological ST changes on exercise testing were included in this study, and none showed significant coronary disease on angiography. None had any evidence of coronary heart disease, cardiac failure, bronchial asthma, or bundle-branch block. All patients had their electrocardiograms recorded in the fasting state, having stopped all drugs in the preceding week.

A Hewlett Packard 1500 B electrocardiogram was used at a paper speed of 25 mm per second and standardised to give a deflection of 10 mm for 1 mV. Symptom-limited exercise testing was performed in the usual manner registering leads III and V5 every minute during exercise and the 10 minute recovery period, using bicycle ergometry (Elema Schonander A-B). Blood pressure was recorded before and during the exercise test and in the recovery period. The first test was performed before and the second repeated one hour after 40 mg oral propanolol in patients who had had a previously positive test. The criteria for a positive exercise test were the development of ST segment depression >1 mm and lasting 80 ms or more.

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Table *Symptoms and findings at rest and during exercise before and after beta blockade*

Case No.	*Age (y)*	*Sex*	*Symptoms*	*Chest pain*	*Resting electrocardiogram*	*Exercise electrocardiogram before beta blockade**	*Exercise electrocardiogram after beta blockade***
1	34	F	—	—	HR 77/min T↓ III	HR 172/min VE	HR 140/min
2	52	M	—	Atypical	HR 68/min T↓ III, flat T aVF	HR 164/min	HR 105/min
3	35	F	—	—	HR 77/min T↓ III	HR 160/min	HR 128/min
4	55	F	Palpitation	Atypical	HR 90/min T↓ III, V5, flat T aVF	HR 164/min	HR 130/min
5	38	M	Palpitation	—	HR 95/min VE	HR 170/min VE	HR 150/min VE
6	33	F	Dyspnoea	—	HR 95/min	HR 166/min	HR 123/min
7	49	F	Dyspnoea	Atypical	HR 82/min, flat T V1-V4 T↓ V5, V6	HR 164/min	HR 126/min
8	54	M	—	—	HR 80/min T↓ III, aVF	HR 164/min	HR 127/min
9	46	F	Palpitation	Atypical	HR 82/min T↓ III	HR 170/min VE	HR 136/min
10	24	F	Palpitation, dyspnoea	—	HR 100/min	HR 180/min	HR 148/min
11	48	F	—	—	HR 77/min, flat T III, aVF	HR 158/min VE	HR 133/min
12	36	F	Palpitation	—	HR 84/min T↓ III, VE	HR 166/min VE	HR 124/min VE

*All patients revealed pathological ST depression.
**None developed ST depression.
VE, ventricular extrasystoles; HR, heart rate.

Results

The Table refers to clinical and electrocardiographic findings at rest and exercise. Nine of the 12 patients (75%) had minor T wave changes predominantly in leads III and aVF. None had resting ST depression. Five patients (41·6%) experienced atypical chest pain during exercise, four (33·3%) complained of dyspnoea, and seven (58·3%) had palpitation. Beta blockers alleviated chest pain in two patients, dyspnoea in one, and palpitation in three. Five patients had ventricular extrasystoles during exercise when un-beta blocked which persisted in two patients after beta blockade. Changes were more prominent on exercise in lead V5. Beta blockade had no significant effect on blood pressure.

Analysis of the pattern of ST depression during exercise without beta blockade showed the following: five (41·6%) developed electrocardiographic abnormalities during early exercise; nine (75%) showed ST changes during the middle of exercise; five (41·6%) showed abnormalities during peak exercise but none originating at this stage; five (41·6%) had abnormalities in the early recovery phase but only in two patients (16·6%) did these changes appear initially at this stage.

Before beta blockade the average resting heart rate was 83·9 beats/min (range: 68 to 100 beats/min); on exercise the average peak rate reached 166·5 beats/min (range: 158 to 180 beats/min). One hour after propranolol the average resting heart rate was 69·4 beats/min (range: 52 to 82 beats/min), 82·7% of that before beta blockade. The peak exercise rate was now 130 beats/min (range: 105 to 150 beats/min), 78% of that before beta blockade. All tracings returned to normal (Fig. 1 and 2) when the exercise test was repeated one hour after oral propranolol. Fig. 3 a and b shows cardiograms from two patients in whom, even though the rate achieved after beta blockade was higher than that at which ST changes appeared before medication, the exercise electrocardiogram failed to disclose ST changes after propranolol.

Discussion

It has been suggested that ethical obligations if not psychological pressure may enforce the performance of coronary angiography on all asymptomatic individuals with exercise-induced ST segment depression.[1] The pressure to undertake coronary angiography is even greater in patients with symptoms and an abnormal exercise test. Mitral valve prolapse is a disorder in which clinical features may mimic those of coronary heart disease and exercise tests are often positive. The prevalence of abnormal exercise tests varies from 10 to 60%[3]; the overall prevalence, however, is in the region of 33%.[4] The risk and high cost of coronary angiography make it unsuitable for general use. Thus, any method that improves the diagnostic accuracy of the electrocardiographic response

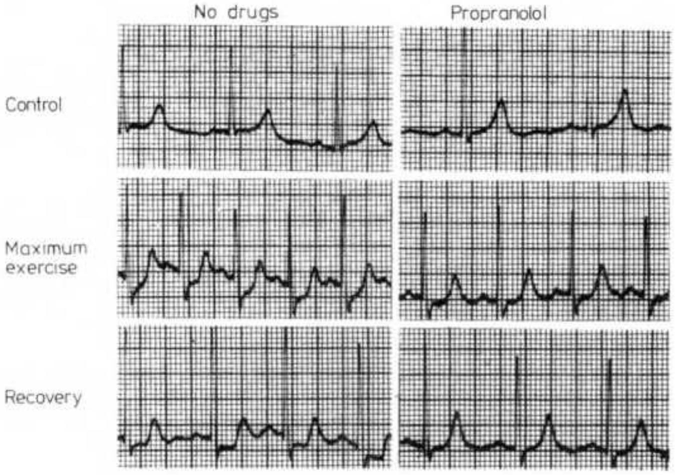

Fig. 1 *Lead V5 of an exercise electrocardiogram of a patient with mitral valve prolapse and anginal type chest pain.* Left—*positive before beta blockade.* Right—*negative, one hour after 40 mg propranolol. Coronary angiogram was normal.*

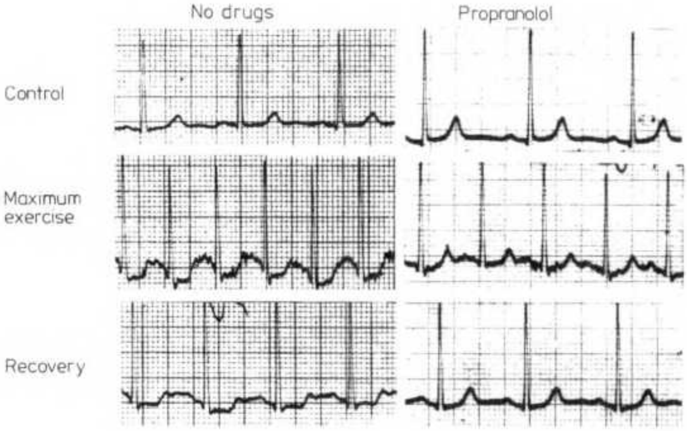

Fig. 2 *Lead V5 of an exercise electrocardiogram of a young woman with mitral valve prolapse and atypical chest discomfort.* Left—*significant ST depression before propranolol.* Right—*normal ST segment one hour after 40 mg propranolol.*

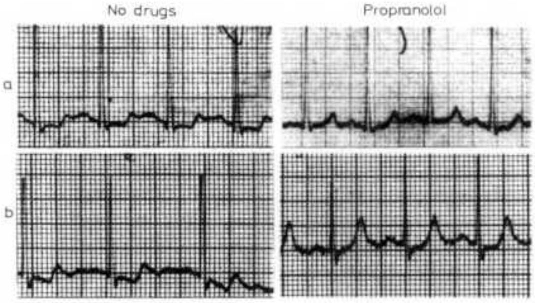

Fig. 3 *Leads V5 of an exercise electrocardiogram of two patients before and after propranolol. Note downsloping ST depression appearing (a) before propranolol at the rate of 109/min and (b) at 82/min. After propranolol no ST depression was observed though the rate in (a) was 119/min and in (b) 100/min.*

to exercise will be valuable in the management of patients in general and those suffering from mitral valve prolapse in particular.

Following an attempt to elucidate the electrocardiographic findings in mitral valve prolapse by the effect of beta blockade on the resting electrocardiogram,[2] sympathetic overactivity as the basis for these electrocardiographic abnormalities and other features related to mitral valve prolapse was studied and later confirmed by metabolic studies.[5] The adequacy of beta blockade in the present study was confirmed by 17 to 22% reduction in resting and exercise heart rates. The exercise response of all patients returned to normal (Fig. 1 and 2). The pronounced "ischaemic" type ST depression appearing at exercise and during recovery returned to normal completely after beta blockade.

Thus our patients with mitral valve prolapse behaved similarly to the non-coronary group reported by Marcomichelakis *et al.*,[6] in which 19 of 20 exercise tests returned to normal after beta blockade in patients none of whom had coronary heart disease or mitral valve prolapse. Exercise electrocardiograms after beta blockade, however, remained positive in 43 of their 44 patients with coronary artery disease; thus specificity and predictive value were improved without reduction in sensitivity. The chronotropic effect of propranolol does not seem to play a significant role as shown in Fig. 3. Two patients showed "ischaemic" ST depression before propranolol at a rate of 109 and 82 a minute, respectively. After propranolol these rates were surpassed, 119 and 100 a minute, respectively, and yet no ST changes appeared.

Twelve out of the 38 patients with mitral valve prolapse who performed an exercise test showed an abnormal result, a prevalence of 31·6%. Though the contour of the ST segment depression was "ischaemic"-like, its behaviour differed from that seen in true ischaemia. Thus, 75% of the patients showed the abnormal response in the middle of the exercise period; the ST depression persisted through the peak exercise stage in only 41·6% of our patients and in none did it originate at this stage.

Our results are in keeping with the thesis that the ischaemic-like electrocardiographic abnormalities in mitral valve prolapse at rest[2] and at exercise are not of coronary origin, but are a consequence of sympathetic overactivity and increased catecholamines or of altered myocardial sensitivity to these amines. Furthermore, exercise-induced electrocardiographic changes resembling those of ischaemia may be mimicked by adrenaline infusion and blocked by oxprenolol.[7]

If our observations are confirmed, the need for coronary angiography will be much reduced in symptomatic patients with mitral valve prolapse and positive exercise tests. We suggest that an exercise test after beta blockade should become part of the routine procedure in investigating such patients. Moreover, by eliminating false positive electrocardiographic responses in this group of patients, the specificity of exercise testing in the investigation of coronary heart disease will be improved.

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Effect of heparin on plasma free fatty acid concentrations after acute myocardial infarction

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SUMMARY Free fatty acid concentrations in plasma measured after in vivo heparinisation are often overestimated because of ex vivo lipolysis of variable degrees. A new method has been developed using immediate extraction of blood which obviates this and shows that the true rise in plasma free fatty acid concentration after heparin in ambulant ward patients and in patients with acute myocardial infarction is less than previously reported. The small rise in plasma free fatty acid concentration after heparin is unlikely to have adverse metabolic effects in most patients during acute myocardial infarction.

In addition to its anticoagulant action heparin has the effect of releasing several lipolytic enzymes into the circulation.[1] These act on circulating triglycerides and phospholipids to release free fatty acids and result in a raised level of plasma free fatty acid concentration. This may have an adverse effect on patients with acute myocardial infarction, as an association has been shown between raised plasma free fatty acid concentrations, serious ventricular arrhythmias, and poor prognosis.[2-4] Increments in plasma free fatty acid concentration after heparin in man have been reported as varying between 750 and 1100 μmol/l.[5 6] Recorded values may be overestimated, however, in view of continuing ex vivo lipolysis before extraction.

The extent of this problem has been assessed by developing a technique of free fatty acid analysis after immediate whole blood extraction to eliminate ex vivo lipolysis, and determining the true heparin-induced rise in plasma free fatty acid concentration in ambulant ward patients and in patients after acute myocardial infarction. Data are compared with those obtained by plasma extraction techniques.

Methods

The time course of plasma free fatty acid concentrations after the intravenous administration of heparin 12 500 international units (IU) was examined in three groups of patients. The first group (randomly selected general ward patients) consisted of nine men and one woman, aged 42 to 63 years. Their weights were between 49 and 99 kg. The patients were studied after overnight fasting. All except one were ambulant and one had known ischaemic heart disease.

The second (n=10) and third (n=10) groups consisted of patients who had had an acute myocardial infarction, and were admitted to the coronary care unit of the Royal Infirmary, Edinburgh. There were 17 men and three women (aged 38 to 69 years). The diagnosis was considered established if the criteria recommended by the World Health Organisation were fulfilled. Patients with a history of bleeding disorders, those in cardiogenic shock (systolic blood pressure <90 mmHg), or those requiring pacing or antiarrhythmic treatment were excluded, as were those on beta blockers or antilipolytic agents.

In a pilot study the effect of intravenous heparin (10 000 IU) was examined on ex vivo lipolysis in eight ambulant ward patients at peak lipaemia approximately two hours after lunch.

Informed consent was obtained from all patients. The study was approved by the local ethical committee.

PROCEDURE

The same procedure was followed in each group of patients. After insertion of a cannula in the antecubital vein, blood samples were taken for estimation of plasma triglyceride and free fatty acid concentrations, both 5 minutes and immediately before

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administration of 12 500 IU heparin intravenously and for estimation of plasma free fatty acid concentrations at five, 10, 15, 30, 45, 60, and 90 minutes after administration of heparin.

Blood samples were processed for free fatty acid estimations in three ways: (1) from one aliquot of the blood sample free fatty acids were extracted immediately without centrifugation using a newly developed method (see laboratory methods); (2) from another aliquot free fatty acids were extracted immediately after separation of plasma and blood cells by a short centrifugation at room temperature, with a four minute delay; (3) another aliquot of the sample was processed using our standard laboratory free fatty acid procedure (20 minute delay).

LABORATORY PROCEDURES

Plasma free fatty acid concentrations were determined using a titrimetric method.[7] To avoid lipolysis in blood samples taken from subjects given heparin, during blood cell separation and processing leading to artificially high plasma free fatty acid concentrations, a new method was developed.[8] Free fatty acids were immediately extracted into n-heptane from a whole blood sample (0·75 ml), as described for plasma samples.[7] Plasma and red cell membrane phospholipids were removed from a 2·0 ml aliquot of the extract by selective adsorption to 200 mg silicic acid.[9] The phospholipid free extract was evaporated under a stream of nitrogen in a heating block set at 60°C. The fatty acids were redissolved in 3 ml chloroform-n-heptane 8:7 (vol/vol) and converted into their ^{63}Ni-salts[10] by addition of 200 μl triethaolamine stabilised ^{63}Ni solution in KBr. Final concentrations: triethanolamine 7·5% (vol/vol); KBr 40·5% (wt/vol); Ni $(NO_3)_2$ 0·5 mmol/l; 63Ni specific activity (NBS 1, Amersham International) 4 mCi/mmol. After vigorous mixing for 15 to 20 seconds, followed by a short centrifugation (5 minutes at 1500 g) to separate the water and chloroform-heptane phases, the radioactive Ni-fatty acid salts in 1 ml of the upper chloroform-heptane phases were analysed by liquid scintillation counting using 9 ml liquid scintillant (NE 260, New England Nuclear). The method was calibrated using 99^{+}% pure palmitic acid standards (British Drug House, Poole) dissolved in heptane, and taken through the extraction procedure.

The concentrations of fatty acids in blood extracts were expressed in terms of plasma concentrations, using a factor based on the packed cell volume, determined in quadruplicate using a Hawksley micro-haematocrit centrifuge.

The extraction of albumin-bound ^{3}H-palmitate added to eight different human blood samples was on average 100·0±1·7% (mean±SEM). More than 94% of pure lecithin (2·75 mg/ml in heptane) was selectively absorbed to silicic acid. Blood lactate concentrations of less than 3·2 mmol/l do not interfere; interferences by higher concentration were not examined.

The precision of the method was assessed by repeatedly (10 times) analysing a palmitic acid standard (400 μmol/l) on two occasions. The coefficients of variations were 6 and 8·5%, respectively.

No statistically significant differences were found when results of the whole blood method were compared with the standard plasma free fatty acid titrimetric procedure in *non-heparinised* subjects, both when plasma free fatty acid concentrations are raised (Fig. 3) or within normal range (Fig. 2 and 4), $p>0·05$ paired t test.

Plasma triglycerides were determined in extracts (0·5 ml), prepared immediately after collection, by an automated fluorimetric method.[11] Appropriate corrections for interference by free glycerol were made. The coefficient of variation of the method was 2%.

In patients with acute myocardial infarction, the vectorcardiogram was monitored in order to assess changes in ST segments as described previously.[12]

Results are expressed as mean±SEM. The effect of heparin on plasma free fatty acid concentrations and differences between results obtained with the three free fatty acid methods were analysed using a paired Student's t test. $P>0·05$ was considered statistically nonsignificant.

Results

EX VIVO LIPOLYSIS AFTER HEPARIN ADMINISTRATION

Ex vivo lipolysis indicated by a rise in plasma free fatty acid concentrations was observed in blood samples obtained 15 minutes after the administration of 10 000 IU heparin to eight ambulant ward patients at peak lipaemia approximately two hours after lunch. Plasma triglyceride concentrations before administration of heparin ranged from 1·3 to 4·4; mean±SD: 3·1±1·0 mmol/l. When blood samples were incubated at room temperature plasma free fatty acid concentrations rose at a rate of approximately 30 μmol/l per min (Fig. 1). Cooling of blood did not prevent the increase in plasma free fatty acid concentration completely and in particular the initial rise was not abolished.

EFFECT OF HEPARIN ON IN VIVO PLASMA FREE FATTY ACID CONCENTRATIONS

An intravenous injection of heparin (12 500 IU) was given after overnight fasting to 10 general ward patients. Plasma free fatty acid concentrations, determined in whole blood extracts, increased in a time dependent manner from 802±104 (range 365 to 1327) to a maximum of 993±95 μmol/l (range 548 to 1368) and returned to pre-heparin values approxi-

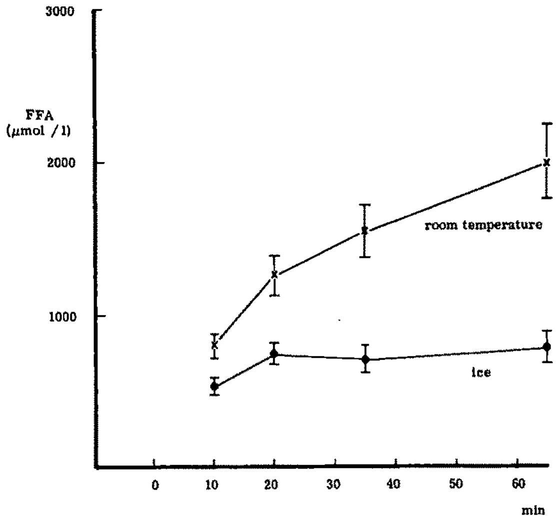

Fig. 1 *Effect of temperature on ex vivo lipolysis in blood samples from postprandial subjects given heparin. Comparison of plasma free fatty acid concentrations in blood samples, taken 15 minutes after 10 000 IU heparin intravenously. (●) Samples stored on ice; (▶) stored at room temperature. Plasma free fatty acids were extracted at the indicated time after collection. Means of seven to eight observations ± SEM. Difference between all pairs is significant (paired t test, $p < 0{\cdot}01$).*

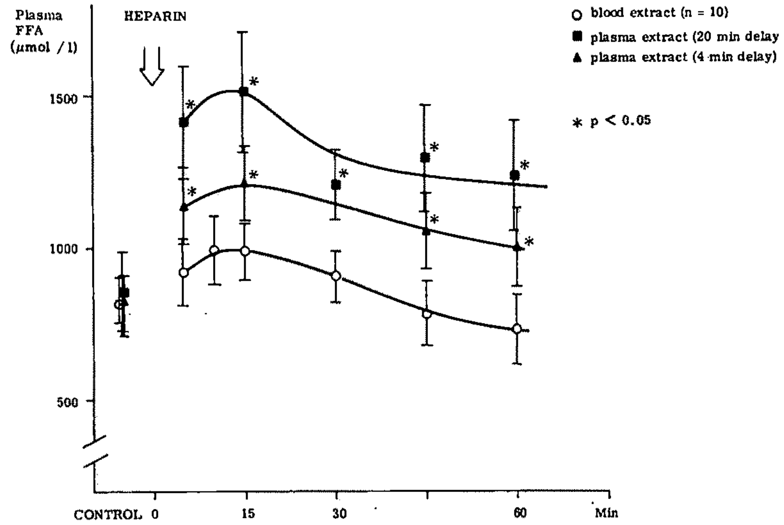

Fig. 2 *The effect of heparin (12 500 IU intravenously) on plasma free fatty acid concentrations in 10 general ward patients after overnight fasting. Comparison of free fatty acid methods: ○ measured in whole blood extracts; ▲ measured titrimetrically in plasma samples extracted within four minutes of blood collection; ■ measured titrimetrically (20 minutes delay).*
Note that before heparin was given free fatty acid concentrations were similar, but after heparin the methods gave significantly different results ($n=8$–10, paired t test $0{\cdot}01 < p < 0{\cdot}05$).

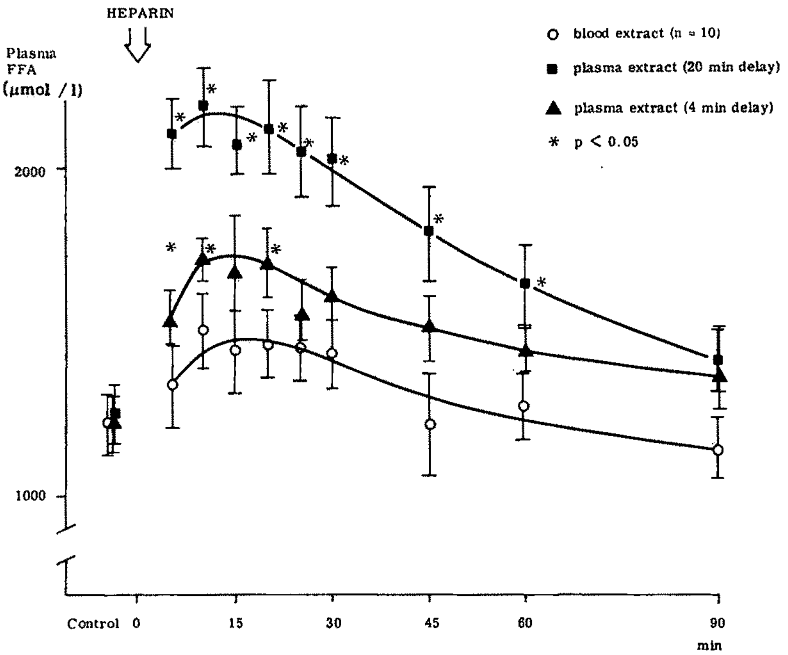

Fig. 3 *The effect of heparin (12 500 IU intravenously) on plasma free fatty acid concentrations in 10 patients with acute myocardial infarction (<6½ hours after onset of symptoms). Symbols as in Fig. 2.*

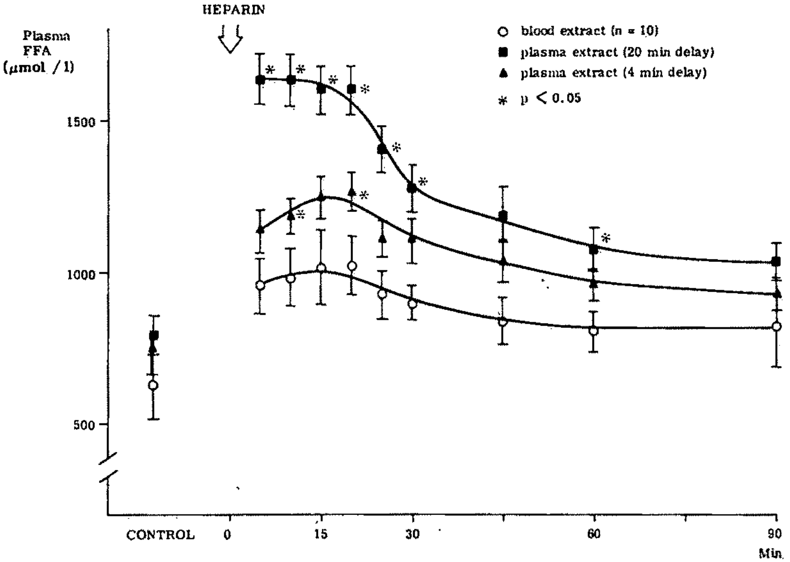

Fig. 4 *The effect of heparin (12 500 IU intravenously) on plasma free fatty acid concentrations in 10 patients with acute myocardial infarction (between 16 and 22 hours after onset of symptoms). Note mean plasma free fatty acid concentrations before heparin are lower than in patients with acute myocardial infarction studied earlier (Fig. 3). Symbols as in Fig. 2.*

mately 45 minutes later (Fig. 2).

Plasma free fatty acid concentrations determined by both whole blood and rapid plasma extraction (four minutes delay) before administration of heparin were not significantly different. After administration, titrimetrically measured levels of heparin were consistently higher than those measured by the whole blood extraction method. Differences in free fatty acid levels recorded between the two methods were significant at all sampling periods after heparin (paired t test, $0{\cdot}01<p<0{\cdot}05$).

When the extraction of plasma samples was delayed by 20 minutes, plasma free fatty acid concentrations were even higher. The increase in plasma free fatty acid concentrations 15 minutes after heparin over the pre-heparin value was then 693 μmol/l. This represents a 260% overestimation of plasma free fatty acid concentrations, when allowance is made for the "true" in vivo increase in the concentrations of plasma free fatty acids of 191 μmol/l (Fig. 2). This overestimation was closely related to the initial plasma triglyceride concentrations ($r=0{\cdot}82$, $n=8$, $p<0{\cdot}01$).

EFFECT OF HEPARIN ON IN VIVO PLASMA FREE FATTY ACID CONCENTRATIONS DURING ACUTE MYOCARDIAL INFARCTION

Plasma free fatty acid concentrations were raised in all patients admitted to the coronary care unit within six and a half hours after onset of symptoms of acute myocardial infarction: 1232±91 μmol/l (upper normal limit is 900 μmol/l) (Fig. 3).

Before administration of heparin plasma free fatty acid values determined by all three methods did not differ significantly. As was observed in general ward patients, plasma free fatty acid concentrations after heparin were overestimated with the standard titrimetric method. The new method on whole blood extracts showed a true increment of 334±73 μmol/l.

In 10 patients the effect of giving heparin was examined (12 500 IU) when plasma free fatty acid concentrations had passed their peak. Plasma free fatty acid levels returned to within the normal range in all but three patients studied between 16 and 22 hours after onset of symptoms. After giving heparin plasma free fatty acid concentrations rose from 658±80 to 983±94 μmol/l within 10 minutes (Fig. 4). This increment was similar to that observed in patients with acute myocardial infarction studied early after the onset of symptoms. Titrimetric analysis overestimated plasma free fatty acid concentrations after heparin also in these patients (Fig. 4).

In six patients with acute myocardial infarction to whom heparin was administered within six and a half hours after the onset of symptoms ST segment vector magnitude was monitored and showed a gradual decline with respect to time before the administration of heparin. This trend was not altered during the course of a transient heparin-induced increase in plasma free fatty acid concentrations (Table).

Table *Effect of heparin on ST segment vector and plasma free fatty acid concentrations in six patients with acute myocardial infarction (<6½ hours)*

	Control	*Heparin*	
		At FFA max	*60 min*
Free fatty acid concentration* (μmol/l)	1243±132	1613±96	1372±132
ST segment vector (mV)	0·18±0·02	0·17±0·03	0·17±0·02

*Determined in whole blood extracts.

Discussion

This study shows that the generally accepted procedures for the estimation of plasma free fatty acid concentrations lead to serious overestimations in subjects given heparin, as a result of in vitro lipolysis. Unless precautions are taken to prevent lipolysis in blood specimens between withdrawal and extraction, artificially high levels are obtained. This observation applies to blood taken from patients with and without acute myocardial infarction, who had been given heparin. In view of the high in vitro lipolytic rate (4%/min at room temperature), it was decided to extract whole blood specimens without processing. This new method will be valuable for studies where accurate measurements of plasma free fatty acid concentrations are imperative.

Using this method we have now shown that in convalescent patients and patients with acute myocardial infarction plasma free fatty acid levels remained well within the physiological range, though plasma free fatty acid concentrations rose after the administration of heparin. The larger rises previously reported[5 6] were mostly the result of delay in denaturing lipolytic enzymes in collected blood samples; in one of these studies[5] plasma triglyceride levels were not measured and it is possible that higher free fatty acid concentrations resulted from higher circulating triglyceride levels. Other studies showing higher plasma free fatty acid concentrations after administration of heparin to patients with coronary artery disease support the view that this error is common.[13 14]

Assessment of "true" plasma free fatty acid concentrations is necessary for understanding the relative importance of the proposed detrimental and beneficial effects of heparin on the ischaemic myocardium. Raised plasma free fatty acid concentrations have been associated with the development of serious ventricular arrhythmias in patients with acute myocardial infarction.[2-4] An hypothesis was proposed that this effect of raised plasma free fatty acid concentrations might lead to serious ventricular arrhythmias as a result of increasing oxygen requirements in the presence of ischaemia or a detergent effect or relative impairment of myocardial glucose metabolism.[15] Raised plasma free fatty acid concentrations exert a negative inotropic effect on the hypoxic or ischaemic myocardium,[16 17] which could offset the increase in myocardial oxygen consumption caused by the metabolic effects of free fatty acids. The relatively small "true" rise in plasma free fatty acid concentrations may explain why in our study and in previous studies heparin did not exacerbate ST segment abnormalities[13 14 18] or increase myocardial oxygen consumption in patients with acute infarction.[14 19]

Heparin may have a protective role in addition to that against venous thromboembolism,[20] by reducing blood viscosity and pulmonary oedema.[21] Recently, it has been claimed to be more effective than beta blockade on short term prognosis.[22] If used in orthodox doses, provided there is no hyperlipidaemia, the metabolic effects on the ischaemic myocardium should be small and it should be safe in most patients when given several hours after the onset of symptoms. Its safety during the most acute phase has yet to be examined formally. In addition, its safety in the presence of hyperlipidaemia must be investigated.

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Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man

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SUMMARY The electrophysiological effects of flecainide acetate (2 mg/kg as an intravenous infusion over five minutes) were assessed in 47 patients undergoing electrophysiological study. Seven patients had normal electrophysiology, 16 had a direct accessory atrioventricular pathway, 12 had dual atrioventricular nodal (AH) pathways, five had paroxysmal ventricular tachycardia, six had conduction system disease, and one patient had a left atrial tachycardia.

No significant change occurred in sinus cycle length. The PA interval, AH interval, and HV interval were all significantly prolonged. The QRS complex duration increased significantly. The QT interval showed slight prolongation due entirely to the increase in QRS duration.

Refractoriness of the atrial and ventricular myocardium was slightly prolonged, but was significant only at ventricular level. No significant change occurred in refractoriness of the normal atrioventricular node. Pronounced prolongation of retrograde "fast" AH pathway refractoriness was observed in those patients with dual AH pathways. Anterograde and retrograde accessory pathway refractoriness were both greatly increased.

These electrophysiological properties strongly suggest that flecainide will be useful in the management of a wide variety of cardiac arrhythmias. It should be administered, however, with caution to patients with pre-existing conduction system disease. Because repolarisation is not delayed flecainide is unlikely to induce ventricular arrhythmias related to prolongation of the QT interval.

Flecainide acetate‡ (N-(2-piperidylmethyl)-2,5-bis (2,2,2-trifluoroethoxy) benzamide acetate) belongs to a unique series of trifluoroethoxybenzamides[1 2] which have proven antiarrhythmic activity against a variety of experimentally induced arrhythmias.[3–5]

Human pharmacokinetic studies have shown that flecainide is almost completely absorbed after oral administration, undergoes minimal hepatic biotransformation, and has a long plasma elimination half-life ranging from 11 to 22 hours,[6 7] properties that are highly desirable for the long term use of antiarrhythmic agents.

This study was undertaken to investigate the acute electrophysiological effects of intravenous flecainide on cardiac conduction and refractoriness in man.

Patients and methods

Forty-seven patients, 27 male and 20 female, whose ages ranged from 16 to 80 (mean 42) years, underwent routine electrophysiological study for the investigation of either symptoms suggesting or documentary evidence of recurrent arrhythmias or cardiac conduction disturbances. The majority of patients with episodes of documented tachycardia had been previously treated with a variety of antiarrhythmic agents. The clinical data are summarised in Table 1.

Seven patients, in whom arrhythmias could not be provoked, were found to have normal cardiac electrophysiology. Sixteen patients had an accessory atrioventricular pathway with atrioventricular reentrant (orthodromic) tachycardia which could be provoked. In eight of these patients accessory pathway conduction was bidirectional with ventricular pre-excitation (Wolff-Parkinson-White syndrome) while the other eight had conduction in the retrograde ventriculoatrial direction alone (that is electrophysiologically concealed). Twelve patients had dual AH conduction pathways with inducible intra

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Table 1 *Patient data*

No of patients	*Age range*	*(mean)*	*Sex*	*Electrophysiological diagnosis*
7	16–60	(43)	5M, 2F	Normal
16	22–73	(41)	10M, 6F	WPW overt 8 concealed 8
12	23–55	(38)	5M, 7F	Dual AH pathways
5	16–36	(27)	2M, 3F	Ventricular tachycardia
6	40–80	(63)	4M, 2F	Conduction delay/block
1	43		M	Left atrial tachycardia

atrioventricular nodal re-entrant tachycardia. Five patients had recurrent paroxysmal ventricular tachycardia and one patient had an intermittent automatic left atrial tachycardia. Six patients underwent electrophysiological study to investigate conduction disturbances involving the sinus node (two patients), atrioventricular node (one patient), or more distal conduction system (three patients).

ELECTROPHYSIOLOGICAL STUDY

All patients were studied in the non-sedated, post-absorptive state after written informed consent was obtained. All antiarrhythmic drugs were discontinued at least three drug elimination half-lives before the electrophysiological study.

Under local anaesthesia (1% lignocaine) and fluoroscopic guidance four or five electrode wires were introduced into the heart. A hexapolar electrode was inserted via the left subclavian vein and positioned with its tip at the right ventricular apex. The two distal poles were used for right ventricular pacing and the four proximal poles were selected to obtain the best possible bipolar recording from the lateral wall of the high right atrium. Where appropriate a quadripolar electrode wire was introduced via the same subclavian vein and positioned in the coronary sinus for recording and stimulation. In the majority of patients these two electrode wires were left in situ at the completion of the acute electrophysiological assessment in order to perform follow-up electrophysiological studies.[8] Two bipolar electrode wires were introduced via a femoral vein. One electrode wire was advanced into the high right atrium for pacing and recording, and the other electrode wire was positioned against the septal leaflet of the tricuspid valve to record His potentials. This "His bundle" electrode wire was adjusted to record distinct low right atrial, His bundle, and right ventricular electrograms.[9] Intracardiac signals were filtered between 50 and 500 Hz and recorded on a 16-channel Siemens-Elema* Mingograf inkjet recorder simultaneously with surface electrocardiographic leads I, aVF, V1, and V6. Paper speeds of 100 and 250 mm/s were used. Intracardiac stimulation was achieved with a Devices† type 4279 "programmable" stimulator using pulse amplitudes at twice diastolic threshold[9] and pulse durations between 1·5 and 2·5 ms. Conduction intervals were studied during sinus rhythm and during constant rate atrial pacing slightly above sinus rate. Anterograde and retrograde conduction characteristics and refractoriness of the heart were determined by the introduction of an extrastimulus after regular atrial or ventricular pacing at a cycle length of 600 ms in most instances.[9, 10]

Incremental atrial pacing from the high right atrium was performed until atrioventricular Wenckebach periodicity occurred or a minimum pacing cycle length of 200 ms was achieved. Incremental ventricular pacing from the right ventricular apex was performed until retrograde ventriculoatrial Wenckebach periodicity occurred or a minimum pacing cycle length of 240 ms was attained. For comparison, characteristics of conduction and refractoriness were measured at identical paced rates and driven cycle lengths before and after flecainide. All intervals were measured to the nearest 5 ms.

FLECAINIDE ADMINISTRATION

After baseline electrophysiological evaluation, flecainide in a dose of 2 mg/kg body weight was administered intravenously over five minutes. Fifteen to 30 minutes after administration of the drug electrophysiological evaluation was made, during which a blood sample was taken for serum flecainide estimation using a sensitive and specific spectrofluorimetric technique described previously.[11]

DEFINITION OF TERMS

Right intra-atrial conduction time (the PA interval) was measured from the onset of earliest atrial activation, on any channel, to the intrinsicoid deflection of the low right atrial electrogram recorded on the His bundle electrode wire.[12–14] Atrioventricular nodal conduction time (the AH interval) was measured from the intrinsicoid deflection of the low right atrial electrogram to the onset of the His bundle deflection.[12–14] His-Purkinje conduction time (the HV interval) was measured from the onset of the His bundle deflection to the earliest onset of ventricular activation.[12–14]

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Intraventricular conduction was measured as the QRS duration from the earliest onset of ventricular activation to the latest J point of the QRS complex in any surface electrocardiographic lead. The QT interval was measured from the earliest onset of ventricular activation to the point at which the latest T wave returned to the isoelectric line. The JT interval during identical rate atrial pacing was used as an index of ventricular repolarisation and was measured from the J point to the point at which the latest T wave returned to the isoelectric line, that is JT=QT—QRS.

Atrioventricular Wenckebach cycle length was defined as the longest atrial cycle length at which anterograde Wenckebach periodicity occurred during incremental atrial pacing.[12-14] Ventriculoatrial Wenckebach cycle length was defined as the longest ventricular cycle length at which retrograde Wenckebach periodicity occurred during incremental ventricular pacing.[9]

Effective refractory period of the atrium was defined as the longest coupling interval of an atrial premature stimulus which failed to cause atrial depolarisation. Effective refractory period of the atrioventricular node was defined as the longest coupling interval of an atrial premature stimulus which failed to cause His bundle depolarisation. Ventricular effective refractory period was defined as the longest coupling interval of a ventricular premature stimulus which failed to cause ventricular depolarisation.[9]

An atrioventricular accessory pathway was defined as a direct atrioventricular connection which bypassed normal atrioventricular nodal and His-Purkinje conduction.[15] Anterograde effective refractory period of an accessory pathway was defined as the longest coupling interval of an atrial premature beat at which block occurred in the accessory pathway with normalisation of the atrial to ventricular activation sequence or at which the atrial premature stimulus failed to conduct to the ventricles. Retrograde effective refractory period of an accessory pathway was defined as the longest coupling interval of a ventricular premature beat at which block occurred in the accessory pathway with normalisation of the retrograde ventricular to atrial activation sequence or at which the ventricular premature stimulus failed to conduct to the atria.

An atrioventricular nodal "fast" pathway was defined as a path which showed the electrophysiological properties of fast, non-decremental conduction and a relatively long refractory period.[16-18] Anterograde effective refractory period of an atrioventricular nodal "fast" pathway was defined as the longest coupling interval of an atrial premature beat at which block in the "fast" pathway occurred with a sudden increase and normalisation of the AH conduction time or at which the atrial extrastimulus failed to conduct to the His bundle and ventricles.[17 18] Retrograde effective refractory period of an atrioventricular nodal "fast" pathway was defined as the longest coupling interval of a ventricular premature beat at which a sudden increase in the retrograde V to A conduction time occurred or at which the ventricular extrastimulus failed to conduct to the atria.

An atrioventricular nodal "slow" pathway was defined as a path demonstrating the electrophysiological properties of slow, decremental conduction with a relatively short effective refractory period.[16-18] Anterograde effective refractory period of an atrioventricular nodal "slow" pathway was defined as the longest coupling interval of an atrial premature beat at which the atrial extrastimulus failed to conduct to the His bundle,[17 18] when anterograde conduction block had previously occurred in the "fast" pathway at longer atrial extrastimulus coupling intervals. Retrograde effective refractory period of an atrioventricular nodal "slow" pathway was defined as the longest coupling interval of a ventricular premature beat at which the ventricular extrastimulus failed to conduct to the atria when retrograde conduction block had previously occurred in the "fast" pathway at longer ventricular extrastimulus coupling intervals.

Accessory pathway and dual AH pathway refractory periods were measured from the same intracavitary positions as close to the pathway as possible before and after drug administration.

STATISTICS

Statistical data were analysed using Student's t test for paired data.

Results

Comparative electrophysiological data are summarised in Tables 2 and 3. All measurements are written as the mean value ± one standard deviation from the mean.

CONDUCTION (TABLE 2)

Flecainide produced a small insignificant decrease in sinus cycle lengths from 745±198 to 734±180 ms. The PA interval prolonged significantly from 41±13 to 50±13 ms; $p<0{\cdot}001$. AH conduction times during sinus rhythm, excluding two patients with overt ventricular pre-excitation which obscured the His potential and the patient with left atrial tachycardia, prolonged from 67±21 to 81±33 ms; $p<0{\cdot}001$. Similar AH prolongation occurred during constant rate atrial pacing slightly faster than sinus rates (84±33 to 101±39 ms; $p<0{\cdot}001$). Flecainide produced complete AH block in one patient with intermittent Wenckebach second degree AV block present before drug administration.

Table 2 *Conduction intervals*

Interval	*No.*	*Control (ms) (mean ±SD)*	*Flecainide (ms) (mean ±SD)*	*Statistical significance (p)*
Sinus cycle length	47	745±198	734±180	NS
PA	43	41±13	50±13	<0·001
AH (SR)	43	67±21	81±33	<0·001
AH (AP)	43	84±33	101±39	<0·001
HV	39	44±9	61±12	<0·001
QRS	47	96±21	118±30	<0·001
QT (SR)	39	368±43	382±44	<0·02
QT (AP)	39	342±25	349±30	<0·01
QTc	39	427±34	446±40	<0·001
JT	39	246±27	232±33	<0·001
WCL (AV)	19	371±153	410±178	<0·05
WCL (VA)	19	355±91	496±72	<0·001

PA, right intra-atrial conduction time; AH (SR), AV nodal conduction time in sinus rhythm; AH (AP), AV nodal conduction time during atrial pacing; HV, H to V conduction time; QRS, QRS duration; QT (SR), QT interval during sinus rhythm; QT (AP), QT interval during atrial pacing; QTc, the corrected QT interval; JT, the JT interval during atrial pacing (QT–QRS); WCL (AV), anterograde Wenckebach periodicity of the AV node; WCL (VA), retrograde Wenckebach periodicity of the AV node.

His-Purkinje conduction times measured in the 39 patients without overt ventricular pre-excitation prolonged considerably from 44±9 to 61±12 ms; $p<0{\cdot}001$ (Fig. 1). After flecainide administration the HV interval prolonged in 37 patients and remained unchanged in two patients. Maximum HV prolongation in any patient was 40 ms. The increment in the HV interval expressed as a percentage of the control HV interval ranged from 0 to 100%, with a mean of 42%. Seventy per cent of patients developed abnormal HV prolongation of greater than 55 ms.[9] One patient with a previously documented episode of complete atrioventricular block, a normal control HV interval, and right bundle-branch block with left anterior hemiblock on his surface electrocardiogram developed complete HV block during flecainide administration. Maximum HV prolongation occurred an average of five minutes after the start of flecainide administration.

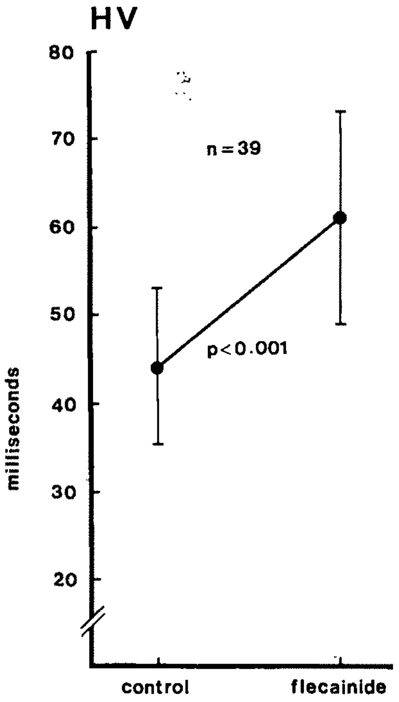

Fig. 1 *The effect of flecainide on the HV interval.*

QRS durations, measured during sinus rhythm in 39 patients and during reciprocating tachycardia in the eight patients with overt ventricular pre-excitation, increased conspicuously from 96±21 to 118±30 ms; $p<0{\cdot}001$ (Fig. 2). QRS durations increased in 44 patients and remained unchanged in three patients. The maximum QRS prolongation was 75 ms in a patient who developed complete right bundle-branch block after flecainide administration. The increment in QRS duration expressed as a percentage of the control QRS duration ranged from 0 to 79%, with a mean of 23%.

QT intervals were compared in the 39 patients without ventricular pre-excitation. The QT intervals during sinus rhythm (368±43 to 382±44 ms; $p<0{\cdot}02$), constant rate atrial pacing (342±25 to 349±30 ms; $p<0{\cdot}01$), and the corrected QT interval derived from Bazett's formula (Q–Tc=Q–T measured/ (R–R interval in s)$^{0\cdot5}$) showed slight significant lengthening (427±34 to 446±40 ms; $p<0{\cdot}001$). The JT interval shortened slightly from 246±27 to 232±33 ms; $p<0{\cdot}001$. Fig. 3 illustrates the typical effect on conduction produced by flecainide.

Flecainide produced complete anterograde accessory pathway block in two patients and complete retrograde block in seven patients, all of whom initially had retrograde accessory pathway conduction only. Retrograde accessory pathway conduction time in the nine patients still capable of retrograde conduction

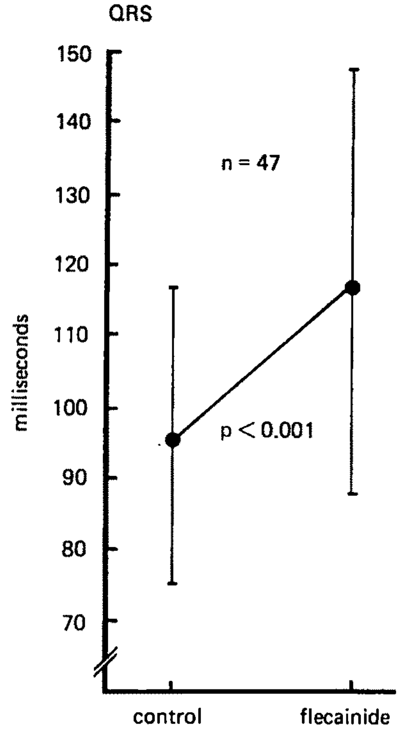

Fig. 2 *The effect of flecainide on QRS duration.*

after flecainide prolonged from 166±51 to 213±60 ms; p<0·01.

WENCKEBACH PERIODICITY (TABLE 2)

Wenckebach periodicity was compared in the 19 patients with normal atrioventricular conduction. The anterograde atrioventricular Wenckebach cycle length prolonged from 371±153 to 410±178 ms; p<0·05, and the retrograde ventriculoatrial Wenckebach cycle length prolonged from 355±91 to 496±72 ms; p<0·001. Two patients developed transient complete atrioventricular block as previously described. Eight patients, however, developed transient complete ventriculoatrial retrograde block after flecainide administration.

REFRACTORINESS (TABLE 3)

(i) *Atrium*

Mean right atrial effective refractory periods increased slightly but did not achieve statistical significance (213±32 to 219±28 ms).

(ii) *Atrioventricular node*

Of the 26 patients with "normal" atrioventricular nodal conduction, excluding the eight patients with overt ventricular pre-excitation, the 12 patients with dual AH pathways, and the patient with intermittent atrioventricular nodal Wenckebach block, assessment of atrioventricular nodal effective refractory period was limited by atrial refractoriness in 16. No significant change in atrioventricular nodal effective refractory period occurred in the remaining 10 patients (314±66 to 287±21 ms)

(iii) *Ventricle*

Right ventricular effective refractory periods prolonged slightly from 220±22 to 229±23 ms; p<0·01.

(iv) *Accessory pathways*

Anterograde atrioventricular accessory pathway refractoriness prolonged significantly from 262±47 to 361±138 ms (p<0·05). Complete anterograde accessory pathway block occurred in two patients. In contrast, atrial effective refractory periods in these eight patients changed insignificantly from 185±22 to 189±25 ms. Retrograde ventriculoatrial accessory pathway refractoriness prolonged more conspicuously

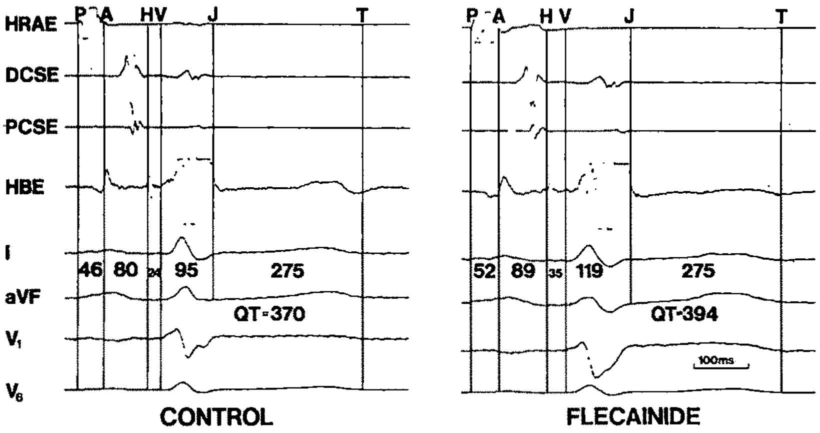

Fig. 3 *Electrocardiographic recordings during sinus rhythm, recorded at 250 mm/s, before (left) and after (right) the administration of flecainide.*

Table 3 *Refractory periods*

Refractory period	*No.*	*Control (ms) (mean±SD)*	*Flecainide (ms) (mean±SD)*	*Statistical significance (p)*
A ERP	47	213±32	219±28	NS
AVN ERP	10	314±66	287±21	NS
V ERP	47	220±22	229±23	<0·01
AHfast (AV)	12	342±59	364±59	NS
AHfast (VA)	11	315±99	450±144	<0·01
AHslow (AV)	6	277±40	293±37	NS
AHslow (VA)	1	280	300	
AP (AV)	8	262±47	361±138	<0·05
AP (VA)	13	300±49	453±169	<0·01

A ERP, atrial effective refractory period; AVN ERP, AV nodal effective refractory period; V ERP, ventricular effective refractory period; AHfast (AV), anterograde refractoriness of "fast" AH pathway; AHfast (VA), retrograde refractoriness of "fast" AH pathway; AHslow (AV), anterograde refractoriness of "slow" AH pathway; AHslow (VA), retrograde refractoriness of "slow" AH pathway; AP (AV), anterograde refractoriness of accessory pathway; AP (VA), retrograde refractoriness of accessory pathway.

from 300±49 to 453±169 ms (p<0·01). Complete retrograde accessory pathway block occurred in seven patients, all of whom had concealed conduction. Ventricular effective refractory periods in these 16 patients changed slightly from 215±22 to 227±24 ms (p<0·01).

(v) *Dual AH pathways*

Anterograde atrioventricular "fast" pathway refractoriness was not significantly affected (342±59 to 364±59 ms). One patient developed complete block in the anterograde "fast" pathway. Retrograde ventriculoatrial "fast" pathway refractoriness prolonged considerably from 315±99 to 450±144 ms (p<0·01). Five out of 12 "fast" pathways showed complete retrograde block after flecainide administration.

No significant changes in refractoriness of the atrioventricular nodal "slow" pathways were observed in either the anterograde or retrograde direction. The majority of "slow" pathway values were, however, limited by atrial refractoriness.

SERUM LEVELS OF FLECAINIDE

Blood for flecainide levels, collected 15 to 30 minutes after drug administration, disclosed serum flecainide levels ranging from 85 to 785 (mean 335) ng/ml. Serum levels of flecainide did not correlate with acute changes observed in conduction intervals or refractory periods.

SIDE EFFECTS

One patient experienced a significant arrhythmia after flecainide administration. This patient, with ventricular pre-excitation, developed ventricular flutter during ventricular extrastimulation after but not before flecainide had been given. Complete AH block occurred in one patient with prior Wenckebach second degree atrioventricular block, and one patient with underlying bifascicular block (right bundle branch block and left anterior hemiblock) developed complete HV block during drug administration. Because of slow ventricular escape rhythms both of these patients required ventricular pacing for periods of 20 to 30 minutes until atrioventricular conduction returned. Minor side effects that occurred only during drug administration included oral paraesthesiae in over 90% of patients and transient drowsiness and dizziness in a small minority. Several patients complained of slight local pain at the site of injection.

Discussion

After initial reports describing the synthesis and antiarrhythmic potential of a series of N-(aminoalkyl) trifluoroethoxybenzamides, one of these compounds, flecainide acetate (R818), has been studied extensively using animal models.[1,2] Its antiarrhythmic potency in dogs, pigs, and mice compared very favourably with reference compounds quinidine, procainamide, and lignocaine when used both parenterally and orally against a variety of experimentally induced supraventricular and ventricular arrhythmias.[3–5]

An evaluation of the intracellular electrophysiological effects of flecainide using isolated rabbit atria showed slowing of conduction velocity and a striking reduction in the maximum rate of depolarisation of the action potential. The effect of flecainide on repolarisation was to produce an alteration in the shape of the action potential without prolonging its duration. Flecainide reduced the spontaneous frequency of sinus node discharge and had a small negative inotropic effect on isolated rabbit atrial muscle.[19]

All of the properties manifested by flecainide are typical of Vaughan Williams Class 1 agents[20] and imply that this drug restricts the fast inward movement of sodium ions.[19]

Initial electrophysiological evaluation in man showed a distinct depressant influence on His-Purkinje and intraventricular conduction, a lesser effect on atrioventricular nodal conduction, and insignificant changes in atrial and ventricular refractoriness. Significant depression of accessory pathway conduction and refractoriness was reported in several patients with the Wolff-Parkinson-White syndrome.[21]

Further human electrophysiological studies combining right ventricular monophasic action potential recordings with programmed ventricular stimulation using larger intravenous doses of flecainide showed significant prolongation of the ventricular effective refractory period concomitant with prolongation of ventricular repolarisation.[22]

The electrophysiological results of the present series show that flecainide significantly depresses conduction within working myocardium and throughout the specialised conduction system. Right atrial conduction was significantly delayed. Ventricular conduction measured by the QRS duration was severely depressed as described by Orning[21] and Olsson and Edvardsson[22] in their initial studies. Atrioventricular nodal conduction times, independent of any rate-related changes in the AH interval, were prolonged by flecainide. The most pronounced effect appeared to be on His-Purkinje conduction where the HV interval prolonged beyond the normal range[9] in 70% of patients after flecainide administration and transient complete HV block occurred in one patient. These changes in cardiac conduction caused by flecainide could be reliably produced in the His-Purkinje system and ventricle but were less predictable in atrial myocardium or the atrioventricular node. Seipel *et al.*[23] also reported similar and dose dependent changes in cardiac conduction when intravenous doses of 2 mg/kg were used.

Slight lengthening of both atrial and ventricular effective refractory periods occurred in the present study group, but only the ventricular refractoriness increased significantly. These findings correlate closely with the findings of Olsson and Edvardsson[22] and indicate that flecainide does have a significant depressant effect on ventricular muscle refractoriness, especially at higher doses. In any one patient, however, a change in atrial refractoriness did not predict a similar change in ventricular refractoriness.

The small increments in QT interval during sinus rhythm, corrected for rate using Bazett's formula, and during constant rate atrial overdrive pacing resulted from QRS widening and not from prolongation of ventricular repolarisation. This is consistent with similar results obtained by Campbell Cowan and Vaughan Williams in their in vitro model.[19] These electrophysiological findings are, however, at variance with the monophasic action potential studies reported by Olsson and Edvardsson where a significant delay of right ventricular repolarisation measured by the monophasic action potentials was observed in their group of nine patients.

The concept of the JT interval was introduced as another index of ventricular repolarisation in order to exclude errors resulting from drug-induced prolongation of ventricular depolarisation. The JT interval did not prolong after flecainide administration which suggests that this drug, unlike quinidine (a Vaughan Williams class 1a drug) or lignocaine (a Vaughan Williams class 1b drug), does not materially affect ventricular repolarisation.

The electrophysiological properties of flecainide do not fall strictly within the modified criteria used to define Vaughan Williams class 1a and class 1b agents.[24] D C Harrison (1981, personal communication) has proposed that a further subgroup, class 1c, should be used to define such drugs including encainide[25] and lorcainide,[26] both of which manifest many electrophysiological similarities to flecainide.

Touboul *et al.*[27] have recently suggested a classification of antiarrhythmic agents according to their electrophysiological characteristics defined by standard electrophysiological assessment. According to this proposed classification flecainide manifests class 3 antiarrhythmic activity, which comprises drugs showing a wide electrophysiological spectrum. In addition to atrioventricular nodal depression they prolong HV conduction times (aprindine[28 29]) or His-Purkinje refractoriness (amiodarone[29 30]). These class 3 drugs may also lengthen refractoriness of accessory pathways and atrial myocardium.

A most profound effect on accessory atrioventricular pathways and "fast" nodal pathways was produced by flecainide. After intravenous administration of the drug complete anterograde block occurred in two out of eight overt accessory atrioventricular pathways and complete retrograde block occurred in seven of 16 accessory atrioventricular pathways. Of the six remaining overt accessory pathways, anterograde refractoriness increased in all cases. Of the nine accessory pathways still capable of retrograde conduction after flecainide administration, refractoriness increased in four patients and in two cases accessory pathway refractoriness slightly shortened. In three cases assessment of accessory pathways refractoriness was limited by ventricular refractoriness.

In the 16 patients with accessory atrioventricular pathways it is of interest that flecainide has such a significant depressant effect on accessory pathway refractoriness compared with the changes in atrial or ventricular myocardial refractoriness in the same patients. These findings suggest that bypass tracts possess electrophysiological characteristics quite distinct from those of atrial or ventricular muscle.

In the 12 patients with dual AH pathways flecainide acetate selectively affected "fast" atrioventricular nodal pathway refractoriness, specifically retrograde refractoriness of this "fast" pathway. Complete retrograde block occurred in five of 12 "fast" pathways. Of the remaining seven patients, "fast" path-retrograde refractoriness was considerably increased in five, unchanged in one, and shortened in the remaining case. Complete anterograde block occurred in only one "fast" pathway. No significant change, however, in anterograde "fast" pathway refractoriness was observed overall. No statistically significant changes in anterograde or retrograde refractoriness of the "slow" pathways were seen though two patients developed complete retrograde ventriculoatrial block of both "fast" and "slow" pathways within the atrioventricular node. The dramatic selective effect of flecainide on "fast" atrioventricular nodal pathway retrograde refractoriness supports the hypothesis of Gomes *et al.*[31 32] and Platt *et al.*[33] that the "fast" atrioventricular nodal pathway possesses quite different electrophysiological characteristics from that of the "slow" or normal atrioventricular nodal pathway.

The electrophysiological effects manifested by flecainide on cardiac conduction, refractoriness, and in particular its effects on accessory pathway and "fast" atrioventricular nodal pathway refractoriness imply that it will be very useful in the management of tachycardias where such conduction and refractoriness are crucial to their continuation, that is atrioventricular nodal and atrioventricular re-entrant tachycardias. Potential problems resulting from conduction failure, however, must be considered particularly in patients with underlying atrioventricular or intraventricular conduction disturbances, or in patients receiving drugs which are known to depress atrioventricular nodal[34 35] or His-Purkinje conduction.[26 28 36]

In conclusion, flecainide acetate clearly manifests the desirable properties of potent depressant effects on cardiac conduction and refractoriness with minimal side effects, suggesting that it may prove a valuable addition to the therapeutic armamentarium in the acute management of a wide variety of cardiac arrhythmias.

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Role of the Frank-Starling mechanism during maximal semisupine exercise after oral atenolol

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SUMMARY Reproducible left ventricular dimensions were found by M-mode echocardiography in eight healthy men in the semisupine position during two maximal bicycle exercise tests, performed with four hours interval. Left ventricular end-diastolic dimension did not increase during maximal exercise, while fractional shortening increased by a decrease in end-systolic dimension. Twelve men studied by the same procedure were given 100 mg atenolol orally just after the first test which conspicuously reduced their heart rate response to exercise. End-diastolic dimension increased significantly from rest to peak exercise after the administration of atenolol in contrast to that before beta blockade, and fractional shortening at maximal exercise increased compared with the preceding control test.

We conclude that atenolol changes the left ventricular response to maximal semisupine exercise in normal man, with dilatation and a concomitant increase in systolic myocardial shortening. This suggests that atenolol during maximal exercise reveals the part played by the Frank-Starling mechanism in cardiac reserve. In addition to that mechanism, the increased ventricular emptying is probably also the result of reduced afterload after administration of atenolol.

The Frank-Starling mechanism signifies a direct relation between end-diastolic length and systolic shortening of myocardial fibres. It is operative in isolated heart preparations,[1 2] left ventricular failure,[3] myocardial infarction,[4] and transplanted hearts.[5] The role of this mechanism concerning the normal left ventricle, however, remains uncertain.[6-8] Cardiac output increases during exercise in normal man[9] as the result of increases in heart rate[9] and stroke volume.[10] It is not clear whether the increment in stroke volume is caused by the decrease in end-systolic[11 12] or the increase in end-diastolic volume (the Frank-Starling mechanism).[7 8] The conflicting data may be attributed to technical limitations, variations in posture, and varying levels of exercise.

Beta adrenergic receptor blockade reduces the exercise response of heart rate and cardiac output,[13 14] but does not reduce the stroke volume.[14 15] This may be compared to the situation in compensated left ventricular failure in which the left ventricle is dilated and stroke volume is maintained. Thus, maintained stroke volume during exercise after beta blockade may suggest operation of the Frank-Starling mechanism.

The internal dimensions of the left ventricle can be measured non-invasively during exercise by echocardiography.[16 17] The purpose of this study was firstly to evaluate the role of the Frank-Starling mechanism in normal men during maximal exercise by this method, and secondly to study whether beta adrenergic receptor blockade would increase or unmask such an effect.

Subjects and methods

A group of eight men not given any drug therapy (age range 24 to 38 years, mean 30 years) and a group of 12 men given atenolol (age range 26 to 38 years, mean 33 years) were studied. Four others were excluded because of the unsatisfactory quality of the echocardiograms. All had normal findings by physical examination at rest, including blood pressure, electrocardiogram, and echocardiogram. None had any history of cardiopulmonary disease. All were physically fit but none participated in competitive athletics. Informed consent was obtained from all subjects before the study.

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BICYCLE EXERCISE

Graded exercise was performed on an electrically braked bicycle ergometer in the semisupine position with a 20° head-up tilt. The initial work load was 50 W for three minutes with subsequent increase by 50 W every three minutes until exhaustion. All subjects performed two exercise tests with an interval of four hours. The highest achieved work load common to both tests was defined as the maximal exercise level for each subject.

BETA ADRENERGIC BLOCKADE

The subjects given atenolol received a single dose, 100 mg orally, within five minutes after the first exercise test. The second exercise test was performed four hours after drug intake, since peak plasma levels occur two to four hours after oral administration.[18]

ECHOCARDIOGRAPHY

M-mode echocardiograms were obtained using an SKI Ekoline 20A Echocardiograph interfaced with a Honeywell strip-chart recorder at paper speed 100 mm/s, with a hand-held 2·25 MHz transducer in the standard intercostal space[19] at the left sternal border. Heart rate was measured from simultaneously recorded electrocardiograms. Measurements were made at the level of the chordae tendineae between the leading edges of echoes from the left border of the interventricular septum and from the posterior wall endocardium. Left ventricular end-diastolic dimension was measured at the onset of the QRS complex and end-systolic dimension on the vertical axis at the peak anterior excursion of the posterior wall (Fig. 1). The measurements were made during expiration and represented the average of at least three heart cycles. Fractional shortening was calculated as (EDD-ESD)/EDD×100% where EDD=end-diastolic dimension and ESD=end-systolic dimension. Recordings were made at rest with the feet on the ergometer pedals, during the last 30 seconds of each exercise level, and at one, three, five, and 10 minutes after termination of exercise, with the feet still on the pedals.

STATISTICAL ANALYSIS

Wilcoxon's two-tailed test for comparison of paired data was used.[20] Differences were considered significant when $p < 0{\cdot}05$.

Results

NO DRUG INTERVENTION

The duration of exercise was 14·1±2·0 (mean±SD) minutes in the first and 13·8±2·1 minutes in the sec-

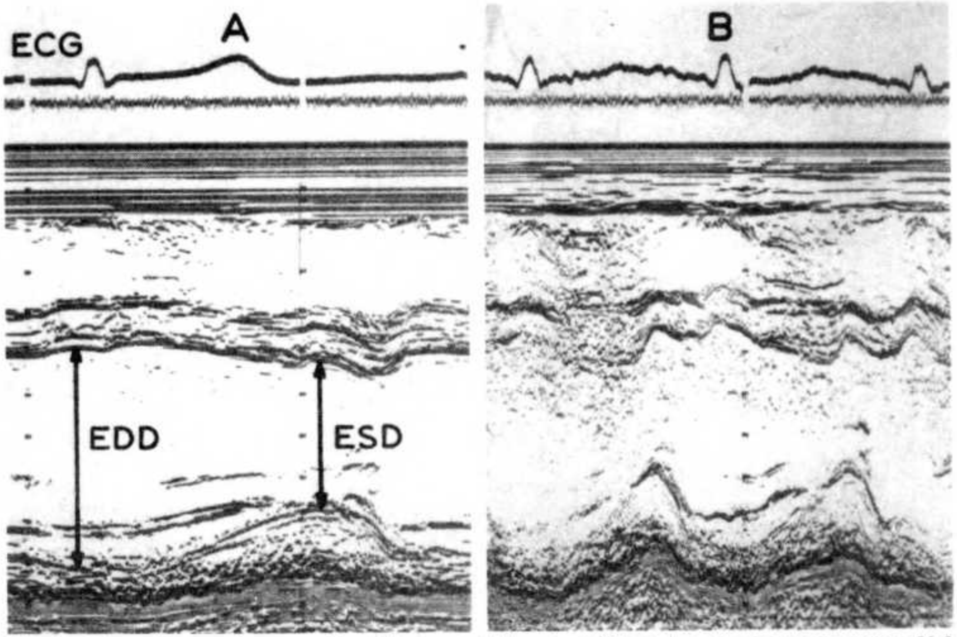

Fig. 1 *Echocardiograms from one subject (A) at rest with heart rate 62 beats/min showing measurements of left ventricular end-diastolic (EDD) and end-systolic dimension (ESD), and (B) during the 13th minute of semisupine bicycle exercise with heart rate 174 beats/min.*

Table 1 *Cardiac response to maximal semisupine exercise without drug intervention (n=8)*

	Heart rate (beats/min)	*EDD (mm)*	*ESD (mm)*	*FS (%)*
First test				
Rest	69±8	50·5±2·7	32·9±2·7	34·9±3·8
Exercise	176±12	49·5±3·1	26·3±5·0	47·8±7·8
p	<0·01	<0·05	<0·01	<0·01
Second test				
Rest	69±6	49·1±3·2	33·1±2·8	32·6±4·0
Exercise	179±9	48·9±2·6	26·9±3·4	44·9±6·4
p	<0·01	NS	<0·05	<0·05

Values are mean ±SD. Abbreviations: EDD, end-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening.

ond test (NS), while the maximal work loads were 256±32 W and 250±38 W, respectively (NS).

Heart rate, left ventricular dimensions, and fractional shortening at rest and maximal exercise in both exercise tests are shown in Table 1. A small reduction in end-diastolic dimension was seen during exercise in the first test (p<0·05) but not in the second test (Table 1). Fractional shortening conspicuously increased in both exercise tests because of a decrease in end-systolic dimension.

Except for a minor difference at six minutes of exercise there were no significant differences in heart rate between the two tests (Fig. 2). There was a 1·4±0·9 mm decrease in end-diastolic dimension at rest from the first to the second test (p<0·05), but the reduction did not exceed 2 mm in any of the subjects. End-diastolic dimension did not differ significantly between the two tests at any exercise level or in the recovery period (Fig. 3). No significant differences between the two tests were found concerning end-systolic dimension (Fig. 3) or fractional shortening (Fig. 4).

BETA ADRENERGIC BLOCKADE

The duration of exercise decreased from 13·8±2·2 minutes before to 12·5±2·0 minutes after atenolol administration (p=0·01), and the maximal work loads were 246±33 W and 229±33 W, respectively (NS).

Heart rate, left ventricular dimensions, and fractional shortening at rest and maximal exercise before and after administration of atenolol are shown in Table 2.

The heart rate was lowered by atenolol at rest, and throughout the exercise and recovery period (Fig. 5). The most pronounced reduction in heart rate was

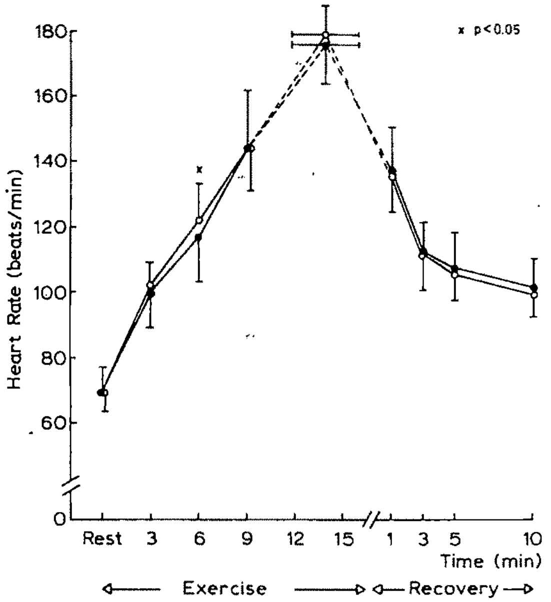

Fig. 2 *Heart rate in eight normal men during maximal bicycle exercise in semisupine position performed with four hours interval. Closed circles = first test. Open circles = second test. Values are mean ± SD.*

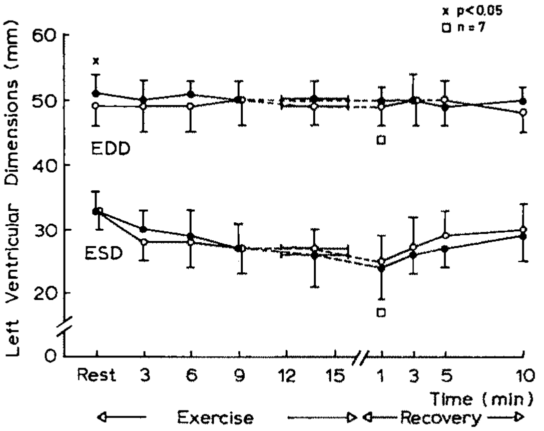

Fig. 3 *Left ventricular end-diastolic (EDD) and end-systolic dimension (ESD) in eight normal men during maximal bicycle exercise in semisupine position performed with four hours interval. Symbols and expression of values as in Fig. 2.*

Table 2 *Effects of atenolol on cardiac response to maximal semisupine exercise (n=12)*

	Heart rate (beats/min)	*EDD (mm)*	*ESD (mm)*	*FS (%)*
Control				
Rest	66±10	50·3±2·6	33·1±2·5	34·7±4·2
Exercise	161±13	51·3±2·9	28·2±3·5	44·9±6·9
p	<0·001	NS	<0·01	<0·01
Atenolol				
Rest	52±6	49·1±2·7	33·4±2·4	31·9±3·5
Exercise	120±9	53·6±3·2	25·6±2·7	52·3±4·5
p	<0·001	<0·001	<0·001	<0·001

Values are mean ±SD. Abbreviations as in Table 1.

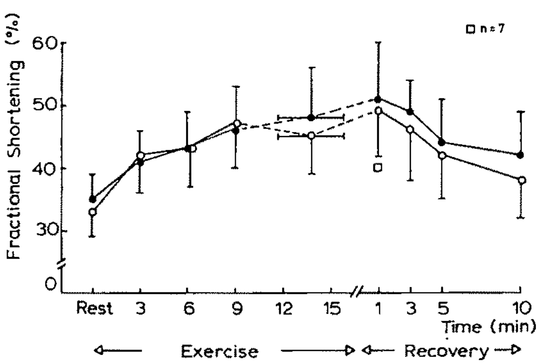

Fig. 4 *Fractional shortening in eight normal men during maximal bicycle exercise in semisupine position performed with four hours interval. Symbols and expression of values as in Fig. 2.*

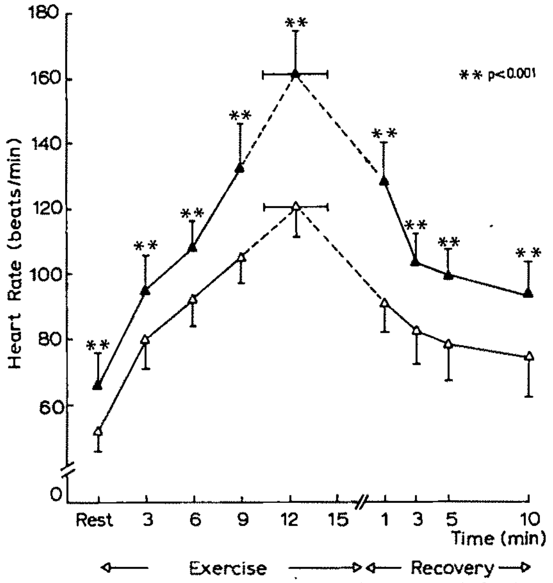

Fig. 5 *Heart rate in 12 normal men during maximal bicycle exercise in semisupine position performed just before (closed triangles) and four hours after 100 mg atenolol orally (open triangles). Values are mean ±SD.*

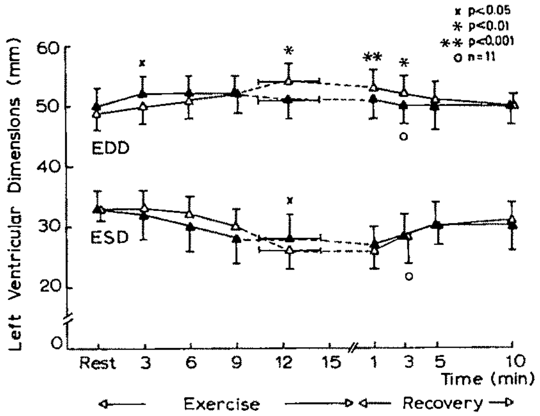

Fig. 6 *Left ventricular end-diastolic (EDD) and end-systolic dimension (ESD) in 12 normal men during maximal bicycle exercise in semisupine position performed just before and four hours after 100 mg atenolol orally. Symbols and expression of values as in Fig. 5.*

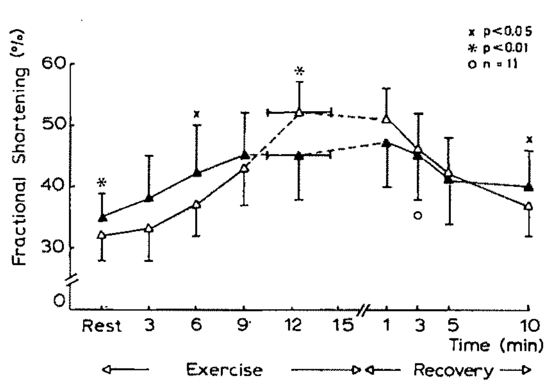

Fig. 7 *Fractional shortening in 12 normal men during maximal exercise in semisupine position performed just before and four hours after 100 mg atenolol orally. Symbols and expression of values as in Fig. 5.*

found at the highest exercise level.

End-diastolic dimension increased significantly from rest to maximal exercise after administration of atenolol in contrast to that before atenolol (Table 2), and was then significantly higher than in the control test at peak exercise and immediately afterwards (Fig. 6). End-systolic dimension was reduced by atenolol only at the maximal exercise level (Fig. 6).

After administration of atenolol, fractional shortening decreased at rest and the lowest exercise levels while it increased at maximal exercise (Fig. 7). The pre-exercise relation with lower fractional shortening after beta blockade was re-established after 10 minutes of recovery.

Discussion

Echocardiography is an accurate and reproducible method for assessment of left ventricular dimensions at rest,[19 21] and, as recently shown, also during exercise.[16] In this study we could show reproducible echocardiographic data when two maximal exercise tests in the semisupine position were performed with an interval of four hours. A small but significant difference in end-diastolic dimension at rest was found between the two tests, but not during exercise or recovery. The difference in end-diastolic dimension, however, was only 1·4 mm and was well within the limits of variation of the method,[19 22] and we therefore do not regard this as representing a real change in left ventricular dimension.

The subjects cycled to exhaustion. Though oxygen uptake was not measured, the exercise level achieved must be regarded as near maximal when considering the heart rate response.[23] The experimental design of this study thus allowed comparison of left ventricular dimensions during maximal exercise before and after drug intervention.

Our finding of reduced end-systolic dimension from rest to maximal exercise without simultaneously increased end-diastolic dimension indicates increased stroke volume by augmentation of left ventricular emptying without left ventricular dilatation. This is in accordance with other echocardiographic investigations,[16 17 24] though lower exercise levels were used in these studies. It is also in agreement with the slight increment in mean pulmonary wedge pressure found in normal men during maximal supine exercise,[25] reflecting a very modest increase in preload. Conflicting results were recently reported, however, in an echocardiographic study where end-diastolic dimension increased during semisupine cycling, with a simultaneous increase in fractional shortening primarily caused by the change in end-diastolic dimension.[7] The lack of a significant decrease in end-systolic dimension at any exercise level compared with rest in that study is in contrast to our findings and those of others.[16 17 24] Increase in end-diastolic dimension during exercise has been found in dogs.[26 27] These studies are, however, probably not directly comparable with the present study since the dogs performed exercise in the standing position while the semisupine position was used in our study.

Atenolol induced an increase in end-diastolic dimension during maximal exercise, indicating dilatation of the left ventricle. The higher fractional shortening at maximal exercise during beta blockade than in the control test probably reflects an increase in systolic myocardial shortening. Our finding of left ventricular dilatation during exercise after beta blockade is in agreement with the distinct increase in left ventricular filling pressure observed in normal men after intravenous administration of propranolol.[14 25] The dilatation cannot be explained by increased afterload since systolic blood pressure during exercise is lower after beta blockade than before.[13 28 29] The decrease in fractional shortening after atenolol at low exercise levels is similar to that found after propranolol in normal subjects who performed mild bicycle exercise in a supine position.[30] At higher exercise levels, we found no indication of a decrease in stroke volume since fractional shortening did not change at moderate exercise and even increased at maximal exercise. Recent radionuclide angiographic studies showed no change in stroke volume during severe exertion after propranolol.[15 25] The stroke index during heavy exercise even increased after long term treatment with atenolol in patients with low grade hypertension.[31]

Our findings indicate increased left ventricular diastolic filling after beta blockade at peak exercise, with a simultaneous increase in systolic myocardial shortening. This suggests that during maximal exercise atenolol shows the part played by the Frank-Starling mechanism in cardiac reserve. Left ventricular performance has been found to be dependent also on changes in afterload, as shown by reduced echocardiographic indices of myocardial shortening in normal human subjects after an acute increase in systolic blood pressure.[32] Thus, the increase in fractional shortening at peak exercise after beta blockade in the present study may also be explained by the easier ventricular emptying caused by decreased afterload, since systolic blood pressure during exercise is reduced by atenolol.[28 29] Systemic vascular resistance in patients with coronary artery disease has been found to increase during rest after the intravenous administration of both propranolol[14] and atenolol.[33] During exercise, however, systemic vascular resistance increased after propranolol[14] but did not change significantly after atenolol,[33] probably reflecting the difference in cardioselectivity between the two beta blockers. It may be speculated that the difference in effect on peripheral resistance during exertion, supposing it is present also in normal subjects, may explain why fractional shortening increased after atenolol during peak exercise in our study in contrast to the reduced ejection fraction during heavy exercise reported after propranolol.[15 25] The increase in fractional shortening might suggest incomplete beta blockade. This is, however, unlikely considering the demonstrated reduction in heart rate at maximal exercise, and since little difference has been found between the effects of 100 and 200 mg atenolol on heart rate during exertion.[34]

The evidence of the Frank-Starling mechanism during exercise after atenolol when the reduction in heart rate became most obvious may be compared to the left ventricular response to exercise in recipients of cardiac transplants. The Frank-Starling mechanism has been shown to be operative in these patients early in exercise when chronotropic and inotropic influences were low because of denervation of the heart.[5] It was, however, not operative later in exercise when levels of circulating catecholamines rose and cardiac output increased by means of tachycardia.

Our findings thus indicate that atenolol discloses the part played by the Frank-Starling mechanism in cardiac reserve with left ventricular dilatation and increased systolic myocardial shortening during maximal semisupine exercise in normal men. The increased ventricular emptying is probably also the result of a reduction in afterload after administration of atenolol.

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Diurnal variation in exercise responses in angina pectoris

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SUMMARY Thirty caucasian male patients with stable angina were investigated in two groups of nine and one group of 12. Nine normal subjects were also studied. Patients in the first group (on no treatment) underwent symptom-limited exercise electrocardiography at 0800, 1200, and 1600 hours on the same day. Their heart rates and ST segment displacements at 1600 hours were significantly greater than at 0800 hours and the same phenomenon was seen in the second group who had been receiving propranolol 40 mg four times a day. A similar effect was noted for ST segment displacement but not for heart rate in the third group (on no treatment) tested at 0800 hours and 1600 hours on separate days, two to three weeks apart. Normal control subjects showed no diurnal variation in heart rate and their heart rate responses at 1600 hours were reduced by propranolol. The observations show a circadian variation in the ST segment response to exercise in patients with angina and a possible training effect on heart rate with multiple exercise testing on the same day. This variation is associated with a reduction in vagal parasympathetic tone to the heart and should be taken into account in the assessment of patients with angina and in particular when comparing responses to treatment.

Circadian variation in cardiovascular variables such as the blood pressure and heart rate is well established.[1 2] Recently, Yasue and co-workers[3] described 13 patients with variant angina in whom there was an angiographically demonstrable increase in tone of the major coronary arteries in the morning when compared with the afternoon. This was associated with a significant variation in exercise tolerance. Little attention appears to have been paid to possible circadian variation in classical angina pectoris and for this reason the clinical impression that a patient's angina is worse in the morning was investigated.

Subjects and methods

Thirty caucasian male patients on no treatment with a history of stable angina pectoris for at least six months were studied in two groups of nine (A and B) and one group of 12 (C). Nine asymptomatic normotensive male volunteers were also studied (D). All the patients were normotensive (BP<160/95 mmHg), had no past history of myocardial infarction, and no evidence of valvular heart disease. They also had a normal chest *x*-ray film and resting electrocardiogram but on exercise using the Bruce treadmill protocol[4] developed at least 1 mm of J point depression with horizontal depression or downslope of the ST segment. These exercise-induced changes have been associated with a 93% specificity for coronary artery disease.[5] Echocardiography was performed to exclude left ventricular or septal hypertrophy and mitral leaflet prolapse as possible causes for false positive exercise electrocardiographic responses. There was no significant difference between the mean ages of the patient groups (56·17±1·71 years overall) or their mean weights (75·67±1·72 kg overall), though the group D subjects were younger (39·39±2·6 years, $p<0·001$). Informed signed consent was obtained from all participants.

EXERCISE TECHNIQUES

All subjects underwent treadmill electrocardiography to angina or exhaustion. An Avionics E10 treadmill was used in conjunction with an Avionics 3000 three

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channel oscillographic monitor. Leads CM4, CM5, and CM6 were studied, recordings being taken automatically at rest, after each minute of exercise, at maximum exercise, and at each of 10 minutes during the recovery period. The chart speed was regularly checked and the recording system optimally damped. The heart rate responses were computed and checked by measurement from the chart. ST segment displacement was noted at 60 ms after the nadir of the S wave by two observers independently, unaware of the circumstances of the test, consensus being obtained with the third.

GROUP A

The patients in group A (on no drugs) underwent exercise electrocardiography at 0800 hours after a light breakfast, at 1200 hours, and at 1600 hours on the same day. A light lunch was taken after the midday test.

GROUP B

The patients in group B were subjected to the same procedure as group A but had received propranolol 40 mg four times a day for at least four weeks before assessment. Drugs were taken on the day of study *after* each exercise recording.

GROUP C

The patients in group C (on no drugs) were randomly allocated into two subgroups. The first underwent a single exercise test at 0800 hours followed by a further single test at 1600 hours, two to three weeks later. The second subgroup started with the 1600 hours test and after two to three weeks underwent a further test at 0800 hours. During analysis both subgroups were combined, randomisation neutralising any changes in performance which might have occurred with training.

GROUP D

The subjects in group D were asymptomatic male colleagues who were randomly allocated into two subgroups. The first subgroup of five underwent the triple procedure while taking no drugs and were retested a mean of four weeks later after receiving propranolol 40 mg four times a day. Drugs were taken during the day of assessment as described for group B. The second subgroup of four received propranolol for at least two weeks before undergoing the triple procedure which was repeated after four weeks on no drugs.

The means and standard error (SEM) of the observations were calculated and the paired observations, that is 0800 hours vs 1600 hours, were examined using Student's paired t test. This technique examines the means of the differences between the paired observations and their relation to zero.

Results

GROUP A

The heart rate responses of this group (on no treatment) are illustrated in Fig. 1. The maximum heart rate was significantly higher in the afternoon than in the morning ($p<0{\cdot}025$), in spite of comparable walking times. The one minute recovery heart rate was also higher ($p<0{\cdot}025$), but the two minute recovery value failed to achieve significance ($0{\cdot}01>p>0{\cdot}05$). The ST segment displacements (Fig. 2) were greater in the afternoon both at maximum heart rate and throughout recovery ($p<0{\cdot}02$ or better), with the exception of the three minute observation ($0{\cdot}01>p>0{\cdot}05$). The 1200 hours observations adopted an intermediate position and, though the walking times at both 1200 hours and 1600 hours were greater than at 0800 hours, the difference was not significant ($0{\cdot}1>p>0{\cdot}05$).

GROUP B

The heart rate responses of this group (who had been receiving propranolol) are shown in Fig. 3. The maximum heart rate was significantly higher in the afternoon ($p<0{\cdot}005$) in spite of the drug, and this difference was good until the end of the third minute of recovery ($p<0{\cdot}025$). Likewise (Fig. 4) the ST segment displacements were greater in the afternoon at maximum exercise ($p<0{\cdot}005$) and after one minute of

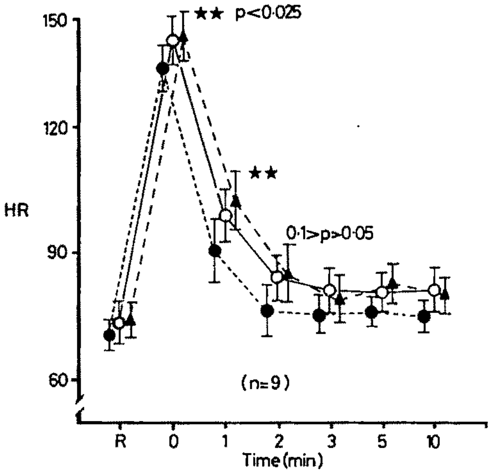

Fig. 1 *Symptom-limited exercise heart rate responses of the group A patients; R (rest); O (maximum heart rate); 1, 2, 3, 5, 10 (minutes of recovery); HR (heart rate). The closed circles represent the means of the 0800 hour values, the open circles those of the 1200 hour values, and the triangles those of the 1600 hour values. The bars represent 1 SEM. The 1600 heart rates are significantly higher at maximum exercise and at one minute of recovery.*

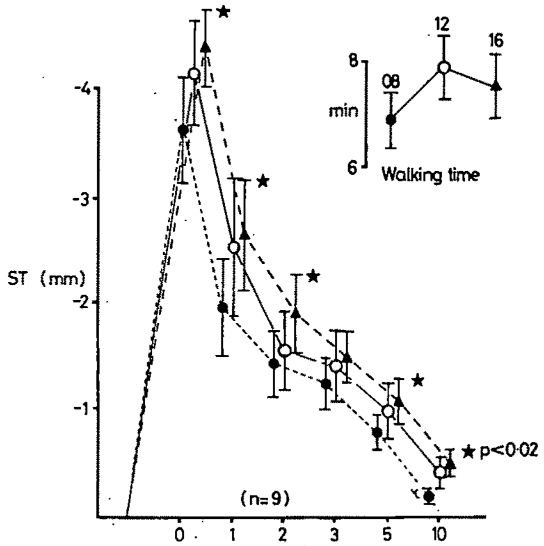

Fig. 2 *ST segment responses of the group A patients illustrated in Fig. 1; the symbols are as for Fig. 1, the ordinate representing millimetres of ST segment depression. The 1600 hours ST segment displacements are significantly greater at maximum heart rate and throughout recovery apart from the third minute.*

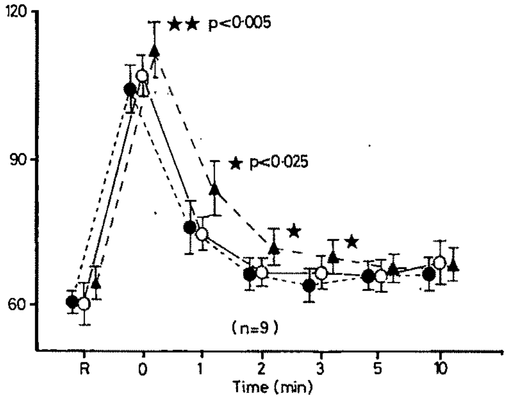

Fig. 3 *Symptom-limited exercise heart rate responses of the group B patients; the symbols are as for Fig. 1. The 1600 hours heart rates are significantly higher at maximum exercise and for the first three minutes of recovery in spite of beta blockade.*

recovery ($p<0{\cdot}05$), the differences thereafter being not significant. No significant difference was seen in the walking times.

GROUP C

The heart rate responses of this group (on no treatment) are illustrated in Fig. 5. No significant differences were seen ($p<0{\cdot}15$). The ST segment displacements observed (Fig. 6) were significantly greater both at maximum heart rate and throughout recovery ($p<0{\cdot}05$ or better) at 1600 hours when compared with 0800 hours.

GROUP D

The heart rate responses of this group when taking no treatment are illustrated in Fig. 7. No significant differences were seen. In sharp contrast to the patients with angina, the afternoon heart rate responses (Fig. 8) were lower when the group received propranolol ($p<0{\cdot}025$ for maximum heart rate through five minutes' recovery; $p<0{\cdot}05$ at 10 minutes).

Discussion

The pathophysiology of ST segment displacement during acute myocardial ischaemia remains uncertain. Angina pectoris in patients with ischaemic heart disease occurs at a reproducible value of rate pressure product[6] in response to exercise and of tension-time index in response to atrial pacing.[7] Exercise-induced ischaemic ST segment depression correlates closely with indices expressing myocardial oxygen consumption (derived from heart rate, blood pressure, and ejection time), but the best single determinant is heart rate[8 9] which was thus used in this study. Nevertheless, variability in exercise tolerance with dislocation of the ST segment/heart rate relation has been described in continued sustained exercise,[10] and with training,[11] and brief severe exercise may be associated with greater triple products at the point of angina than after more limited exercise.[12] Detry *et al.*[13 14] sub-

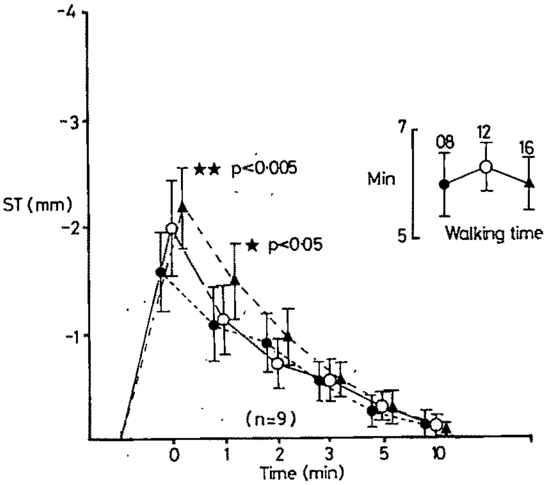

Fig. 4 *ST segment responses of the group B patients illustrated in Fig. 3; the symbols are as for Fig. 1 and 2. The 1600 hours ST segment displacements are significantly greater at maximum heart rate and during the first minute of recovery.*

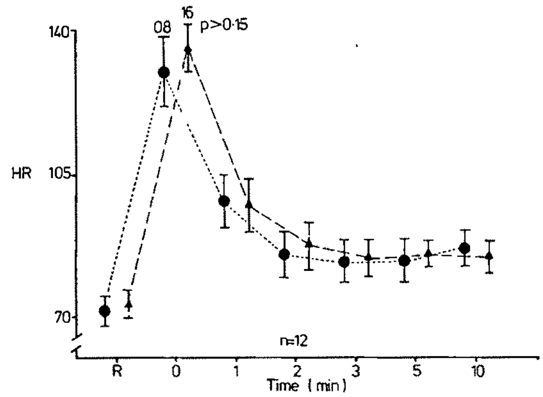

Fig. 5 *Symptom-limited exercise heart rate responses of the group C patients exercised on one occasion on each of two days, two to three weeks apart; the symbols are as for Fig. 1. No significant difference was observed between the pairs of observations at any point.*

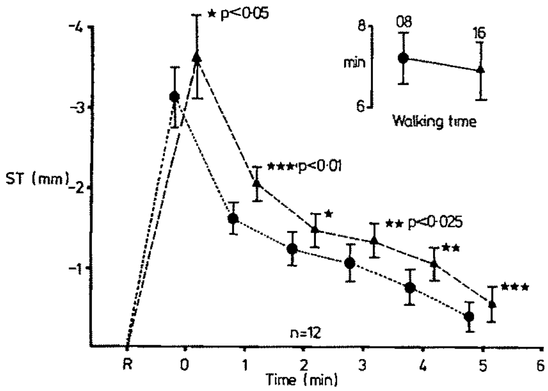

Fig. 6 *ST segment displacements of the group C patients illustrated in Fig. 5; the symbols are as for Fig. 1 and 2. The 1600 hours ST segment displacements are significantly greater at maximum heart rate and throughout recovery.*

jected patients with angina to a three month training routine and observed a significant decrease in heart rate and pressure rate product at submaximal exercise, but at maximal exertion these values were greater and associated with increased ST segment displacement. These investigators suggested that training could raise the threshold for angina. Sim and Neill[15] also confirmed a higher threshold for angina induced by exercise after training but not during atrial pacing. The heart rate and ST segment observations in group A are equally consistent with an exercise-induced functional adaptation or with a circadian variation in exercise performance. The group C patients who underwent a single 0800 hours exercise test followed by a further test two to three weeks later showed greater ST segment displacements at 1600 hours, suggesting a circadian variation in tolerance of myocardial ischaemia if ST segment displacement reflects myocardial oxygen deficit and the pathogenesis of pain.[8] The heart rate response at 1600 hours in group

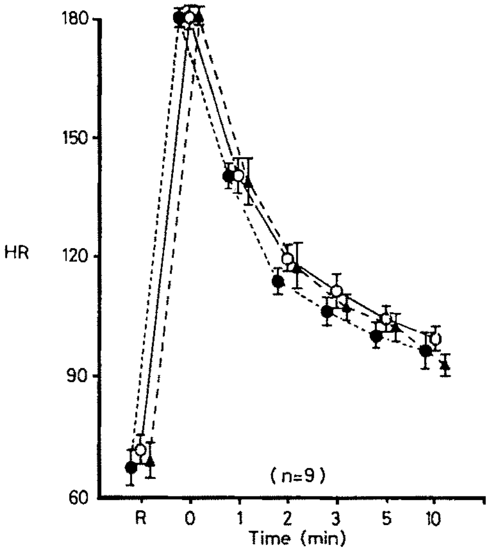

Fig. 7 *Symptom-limited exercise heart rate responses of the normal subjects in group D, on no treatment; the symbols are as for Fig. 1. No diurnal variation is seen.*

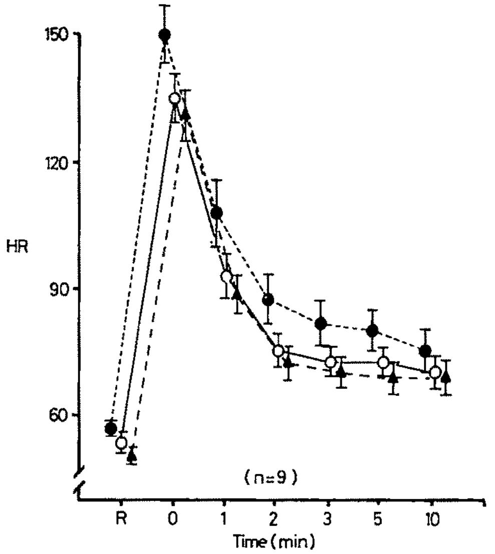

Fig. 8 *Symptom-limited exercise heart rate responses of the normal subjects in group D illustrated in Fig. 7 after two to four weeks' treatment with propranolol 40 mg qds; the symbols are as for Fig. 1. The 1600 hour heart rates are significantly lower than the 0800 hour heart rates at maximum exercise and throughout recovery.*

A, not shown by group C, may be explained by a training dependent adaptation[15] which does not occur in normal subjects off treatment (Fig. 7). The pattern of enhanced heart rate responses and ST segment displacements seen in group A was also seen in group B, in spite of treatment with propranolol (Fig. 3, 4), though this beta adrenoceptor blocking agent reduced the heart rate response of the normal subjects (Fig. 8), as would be expected.

It may be inferred that the normal subjects receiving propranolol (Fig. 8) have a reduced heart rate response to exercise because of reduction in sympathetic drive to the heart, vagal parasympathetic withdrawal being complete at maximal exercise. In contrast, the higher heart rate responses at 1600 hours in group B can only be explained on the basis of a withdrawal of vagal tone unless the unlikely circumstance of sympathetic overdrive is proposed. The circadian variation in ST segment displacement and the exercise dependent adaptation of the heart rate are thus associated with or mediated by a reduction in vagal tone to the heart. Yasue *et al.*[3] showed a circadian variation in exercise capability in patients with variant angina, and using angiographic techniques convincingly showed an increase in tone of the major coronary arteries in the morning, compared with the afternoon. Though there is evidence that metabolic effects[16] and local oxygen concentration[17] are prime determinants of coronary artery tone, evidence for neurogenic influence is available,[18] which may involve the parasympathetic nervous system.[19] It is therefore interesting to note that the variation in exercise responses in subjects with angina observed above is associated with or mediated by changes in parasympathetic tone to the heart. Such variations in exercise response have implications when exercise electrocardiography is used to monitor patient progress or study responses to treatment.

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Influence of R wave analysis upon diagnostic accuracy of exercise testing in women

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SUMMARY Exercise electrocardiography in women with chest pain is associated with a high incidence of false positive ST segment depression. The recent observation that changes in R wave amplitude during exercise can also be used diagnostically may improve the value of stress testing in women. The results of 12 lead treadmill exercise and coronary angiography were reviewed in 62 women, mean age 51 years, presenting with "angina" without previous myocardial infarction. These were compared with exercise results in 14 healthy asymptomatic volunteers with a mean age of 26 years. In addition to conventional ST analysis, R wave amplitude changes during exercise, measured in leads II, III, aVF, and V4 to 6, were examined. While the sensitivity and specificity of ST and R wave changes were similar at about 67%, their combined interpretation was helpful. If both ST and R wave criteria were negative the predictive accuracy for normal coronary angiography was 94% (17/18). Alternatively, in tests showing both ST depression and an abnormal R wave response, coronary angiography was always abnormal (13/13). None of the normal volunteers developed ST segment depression and 93% (13/14) had a normal R wave response. If both were positive, however, coronary angiography was always abnormal (13/13).

Although stress test interpretation in women is difficult, R wave analysis is a useful adjunct to ST change and can improve the predictive accuracy of the test in a significant number of patients.

Conventional interpretation of an exercise electrocardiogram using ST segment analysis in women with chest pain may show many falsely positive tests when judged by the results of coronary angiography.[1-7] Women have a lower prevalence of occlusive disease, however,[8 9] and the use of coronary artery stenosis as the ultimate standard for comparison may be inappropriate. Small vessel disease, reduced coronary dilatory capacity, coronary spasm, inadequate arterial size, cardiomyopathy, abnormal oxygen dissociation, psychosomatic aetiology, and angiographic misinterpretation have been put forward to explain the association of angina-like chest pain and "normal" coronary arteries in women.[1-7 10 11] Even though the prognosis of the syndrome is good,[10] many women undergo coronary angiography, with the attendant risk of morbidity, to exclude coronary artery stenosis. There remains a requirement for improved non-invasive diagnosis in this difficult group of patients.

R wave amplitude decreases during the course of a normal exercise test[12-15] and it seemed possible that adding R wave analysis to conventional ST analysis would increase the diagnostic accuracy of stress testing in women. The object of this study was to examine the influence of R wave amplitude change on the interpretation of 12 lead treadmill exercise electrocardiograms in women admitted to the National Heart Hospital for coronary angiography during investigation for chest pain. All women having both exercise tests and angiography, without electrocardiographic evidence of previous myocardial infarction, were reviewed irrespective of their exercise performance to provide an evaluation of both the diagnostic criteria and the exercise test. The results were compared with those in a small group of healthy asymptomatic young women.

Subjects and methods

Since 1978, 275 women have undergone diagnostic 12 lead exercise testing at the National Heart Hospital. All women who had had cardiac catheterisation in addition were eligible for this study. We excluded

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Table 1 *Exercise test results in 14 normal volunteers*

Subject	*Age (y)*	*Duration of exercise (min)*	*ΣR (rest)*	*ΣR (peak)*	*% Δ R*	*Peak heart rate*
1	29	18	10·95	8·25	−25	188
2	23	15	7·8	4·65	−40	182
3	23	15	10·90	9·90	− 9	150
4	25	14	3·75	4·60	+23*	188
5	21	12	9·40	7·80	−17	180
6	30	13	8·90	6·95	−22	160
7	23	12	3·10	1·20	−61	184
8	28	15	6·8	4·50	−34	164
9	27	17	8·25	7·80	− 5	168
10	30	15	8·20	7·40	−10	122
11	21	14	10·80	8·35	−23	178
12	20	15	7·70	6·25	−19	172
13	24	15	5·20	3·90	−25	180
14	35	15	3·30	1·70	−48	180
Mean	26	14	7·50	5·95	−23	171
(SEM)	1	0·4	0·7	0·7	5	5

Σ R (rest)=six lead R wave sum (leads II, III, aVF, V4 to 6), recorded at rest in the erect position and expressed in mV.
Σ R (peak)=six lead R wave sum in the same leads at peak exercise.
% Δ R=(ΣR(rest)−ΣR(peak)) as percentage change from ΣR(rest).
*=Abnormal R wave response to exercise.

Table 2 *Distribution of clinical findings related to presence or absence of coronary artery stenosis*

Coronary artery disease (n=27)		*No fixed coronary stenosis (n=35)*
25 (93%)	Angina	23 (66%)
22 (81%)	Beta blockade	13 (37%)
13 (48%)	Normal electrocardiogram (at rest)	21 (60%)

those who had electrocardiographic evidence of prior myocardial infarction, conduction defects such as bundle-branch block or atrial fibrillation, and those taking digoxin, or with associated rheumatic or congenital heart disease, or hypertrophic cardiomyopathy.

Sixty two women, aged 29 to 64 (mean age 51 years), fulfilled the study criteria. They all presented with chest pain. Thirty four (55%) had a normal resting electrocardiogram, with the remainder showing only repolarisation changes. Forty eight (77%) were thought to have classical angina pectoris with the rest classified by the admitting physician as either probable or atypical angina. Thirty five (56%) had taken a beta blocking drug within 48 hours of the exercise test. The results were compared with the findings in 14 healthy asymptomatic female volunteers aged 21 to 35 (mean 27) years who were not taking drugs and in whom cardiovascular examination was normal.

EXERCISE TESTING AND INTERPRETATION

The 12 leads chosen were the same as for a standard electrocardiogram with the limb leads attached to the trunk close to the limb in question. Recordings were made in the erect position at rest and at three minute intervals during exercise, at peak exercise, and every one to two minutes during recovery. The Bruce protocol was used, modified by the addition of a warm-up stage of 1 mph at 5% grade.[16] Each electrocardiogram was recorded on a fully automated three channel recorder (either Cambridge Instruments model 3038 or Hewlett Packard model 1517). The recording equipment and exercise procedures complied with American Heart Association standards.[17 18]

Each exercise test was examined without knowledge of the results of cardiac catheterisation. ST segment and R wave amplitude changes were analysed. ST change was considered positive if there was at least 0·1 mV horizontal or downsloping depression, from rest, for at least 80 ms after the J point. R wave amplitude was measured in six leads (II, III, aVF, V4 to 6) in each electrocardiogram and considered abnormal if the peak exercise six lead sum failed to show a 5% decrease when compared with the resting value. A fall in systolic blood pressure of 10 mmHg or more from the resting level during exercise was also regarded as a positive indicator of disease even without additional electrocardiographic abnormalities.

ANGIOGRAPHY

Left ventricular and coronary angiography were performed by the Sones technique. Stenosis of a major coronary artery was considered significant if there was greater than 50% narrowing of the diameter.

Results are expressed, where necessary, as mean (± SEM) and analysis performed using χ^2 or Student's t test for paired and unpaired samples.

Table 3 *Exercise test results using ST segment depression or R wave amplitude change alone or in combination*

	True positive	*False negative*	*True negative*	*False positive*	*Sensitivity*	*Specificity*	*Predictive accuracy*	
							Positive	*Negative*
ST depression	18	9	26	9	67%	74%	67%	74%
R wave change	18	9	23	12	67%	65%	60%	72%
ST −ve and R wave −ve		1*	17			49%		94%
ST +ve and R wave +ve	11			2†	41%		85%	

*Patient with non-dominant right coronary disease.
†Both patients with unprovoked coronary spasm during coronary angiography.

Table 4 *Findings in 18 women showing both no ST segment depression and decreased R wave amplitude at peak exercise*

Patient	*Age (y)*	*Duration of exercise (min)*	*HRmax*	*ΣR (rest)*	*ΣR (peak)*	*% Δ R*	*ST*	*Angio*
15	54	8	168	6·0	4·4	−27	—	N
16	50	12	190	7·45	5·55	−26	—	N
17	42	10·5	156	11·00	9·50	−14	—	N
18	52	12	155	7·25	6·40	−12	—	N
19	39	12·5	160	6·70	5·45	−19	—	N
20	51	7	156	4·65	3·45	−26	—	N
21	35	12	180	6·35	6·00	− 6	—	N
22	29	10	132	10·10	9·50	− 6	—	N
23	39	12	150	7·45	6·80	−11	—	N
24	43	11·5	152	7·70	6·15	−20	—	N
25	47	12	160	10·40	8·00	−23	—	N
26	54	11·5	160	2·10	1·75	−17	—	N
27	51	12	132	6·60	5·70	−14	—	N
28	33	6	85	4·20	3·90	− 7	—	N
29	48	12	100	6·30	6·00	− 5	—	N
30	43	12	160	7·50	6·80	− 9	—	N
31	46	13	170	7·55	6·65	−12	—	N
32	57	10	120	6·50	6·10	− 6	—	1VD
Mean	45	10·9	149	6·99	6·01	−14		
(SEM)	2	0·5	6	0·5	0·5	2		

HRmax = peak heart rate attained during exercise.
Σ R (rest) = six lead R wave sum (leads II, III, aVF, V4 to 6), recorded at rest in the erect position and expressed in mV.
Σ R (peak) = six lead R wave sum in the same leads at peak exercise.
% Δ R = (ΣR(rest)−ΣRT(peak)) as percentage change from ΣR(rest).
*Abnormal R wave response to exercise.
**Systolic hypotension at the end-point of exercise.

ST = Results of ST segment analysis at peak exercise.
 − = Negative test.
 A = Positive anterior (V2 to 4) ST depression.
 L = Positive lateral (I, aVL, V5, V6) depression.
 I = Positive inferior (II, III, aVF) depression.

Angio = Results of coronary angiography in each patient.
 N = Normal.
 1VD = Single vessel disease.
 2VD = Double vessel disease.
 3VD = Triple vessel disease.
 AbLV = Abnormal ventriculogram, normal coronary angiography.
 APT = Abnormal atrial pacing test.
 PMV = Prolapse of mitral valve.
 Spasm = Unprovoked variation of coronary calibre without demonstrable coronary stenosis.

Results

NORMAL VOLUNTEERS

These 14 normal women achieved a peak heart rate of 171±5 bpm, with no evidence of ST segment depression. The average exercise duration was 14·6±0·4 minutes. R wave amplitude decreased from 7·50±0·7 mV at rest to 5·95±0·7 mV at peak exercise (t=5·7, p<0·001). This mean decrease of the resting value was 23%. All but one of the women showed decreased R wave height, ranging from 5 to 61% of the resting amplitude (Table 1).

PATIENTS

Twenty seven women had coronary artery stenosis (10 single vessel, eight double vessel, and nine triple vessel disease). Thirty five women had no evidence of fixed coronary artery stenosis on angiography, though

Table 5A *Findings in 15 women without angiographic evidence of coronary stenosis having exercise test result showing either ST depression or abnormal R wave response*

Patient	*Age (y)*	*Duration of exercise (min)*	*HRmax*	*ΣR (rest)*	*ΣR (peak)*	*% Δ R*	*ST*	*Angio*
33	57	7·5	146	6·00	6·10	0 *	—	N
34	43	9·0	176	3·10	3·10	0 *	—	N
35	54	12·5	160	5·90	5·90	0 *	—	N
36	53	7·0	74	9·10	8·30	− 9	I	N
37	43	15·0	142	6·40	5·20	−19	I	N
38	54	9·0	170	7·00	6·15	−12	I	N
39	59	9·0	130	4·45	5·00	+12 *	—	N
40	58	3·0	80	4·25	5·05	+19 *	—	N
41	59	1·5	130	5·90	6·20	+ 5 *	—	N
42	48	4·0	126	6·55	7·50	+15 *	—	N
43	58	8·0	100	5·95	6·30	+ 6 *	—	AbLV
44	47	12·0	85	3·60	3·30	− 8	L	APT
45	56	9·5	156	5·00	5·40	+ 8 *	—	APT
46	48	9·5	130	11·70	9·30	−21	I	APT
47	51	12·0	145	10·50	9·60	−10	IL	PMV
Mean	53	9·5	130	6·36	6·16	− 1		
(SEM)	6	0·9	8	0·6	0·5	3		

HRmax = peak heart rate attained during exercise.
Σ R (rest) = six lead R wave sum (leads II, III, aVF, V4 to 6), recorded at rest in the erect position and expressed in mV.
Σ R (peak) = six lead R wave sum in the same leads at peak exercise.
% Δ R = (ΣR(rest)−ΣRT(peak)) as percentage change from ΣR(rest).
*Abnormal R wave response to exercise.
**Systolic hypotension at the end-point of exercise.

ST = Results of ST segment analysis at peak exercise.
− = Negative test.
A = Positive anterior (V2 to 4) ST depression.
L = Positive lateral (I, aVL, V5, V6) depression.
I = Positive inferior (II, III, aVF) depression.

Angio = Results of coronary angiography in each patient.
N = Normal.
1VD = Single vessel disease.
2VD = Double vessel disease.
3VD = Triple vessel disease.
AbLV = Abnormal ventriculogram, normal coronary angiography.
APT = Abnormal atrial pacing test.
PMV = Prolapse of mitral valve.
Spasm = Unprovoked variation of coronary calibre without demonstrable coronary stenosis.

Table 5B *Findings in 16 women with proven coronary stenosis and exercise test showing either ST depression or abnormal R wave response*

Patient	*Age (y)*	*Duration of exercise (min)*	*HRmax*	*ΣR(rest)*	*ΣR(peak)*	*% Δ R*	*ST*	*Angio*
48	47	10	100	8·30	7·40	−11	IL	1VD
49	48	6	75	6·70	6·50	− 3 *	—	1VD
50	46	8	150	7·35	7·35	0 *	—	1VD
51	44	7	155	5·60	5·20	− 7	I	1VD
52	50	13·5	145	3·65	2·90	−21	IL	1VD
53	57	6	92	6·70	8·40	+25 *	—	1VD
54	50	6	96	11·55	11·65	0 *	—	1VD
55	58	7	98	8·15	6·50	−20	IL	2VD
56	58	5·5	145	2·70	1·70	−37	L	2VD
57	58	10	132	7·10	5·40	−24	IL	2VD
58	38	15	122	6·20	5·70	− 8	IL	2VD
59	59	5	60	7·35	7·35	0 **	—	2VD
60	63	9	90	10·10	10·60	+ 5 *	—	2VD
61	56	6	78	2·45	1·85	−24	I	3VD
62	63	10	90	5·30	5·90	+11 *	—	3VD
63	55	4	80	7·65	7·65	0 **	—	3VD
Mean	53	8	107	6·68	6·38	− 7		
(SEM)	7	0·8	8	0·60	0·70	4		

For explanation to abbreviations see footnote to Table 5A.

seven (20%) showed other abnormalities comprising severe coronary spasm in two, abnormal left ventriculography in one, mitral prolapse without regurgitation in one, and an abnormal pacing stress test (ST depression and chest pain or raised left ventricular end-diastolic pressure) in three patients (of four who had an atrial pacing test). The distribution of clinical findings related to the results of angiography is shown in Table 2.

EXERCISE TEST

The sensitivity and specificity of ST or R wave changes were lower than we would expect from exercise testing of our typical hospital population,[19] and the predictive values of 60 to 70% are not clinically useful (Table 3). When both criteria were employed, that is with both negative ST and reduced R wave amplitude in the same test, there was a 94% predictive accuracy for normal coronaries though specificity was only 49%. Likewise, the doubly positive test had a low sensitivity but a high predictive accuracy (Table 3).

Individual results for all the patients are shown in Tables 4, 5, and 6, arranged according to the findings of the exercise test. Of the 18 test results fulfilling both negative criteria, 17 had normal coronary angiography, with the remaining patient having non-dominant right coronary disease (Table 4). The results in this group are similar to those in the normal volunteers (Table 1) with the significantly lower exercise duration (10·9±0·5 versus 14·6±0·4 min, $p<0·001$) and maximum heart rate (149±6 versus 171±5, $p<0·01$) reflecting the difference in age between the two groups.

In contrast, the remaining patients shown to have no coronary stenosis had either an abnormal R wave response (in nine) or "false" ST segment depression (in six women) (Table 5a). Five patients in this subgroup had abnormalities other than coronary stenosis. The abnormal R wave response was not the result of a poor chronotropic response as the mean peak heart rate in those nine patients was 134±10 which is 86%±6% of the predicted age related maximum.

Sixteen (59%) of those with coronary disease had either ST depression or an abnormal R wave response to exercise (Table 5b). Comparison of Tables 5a and 5b shows significant difference only with respect to

Table 6 *Findings in 13 women with exercise tests showing both ST depression and abnormal R wave amplitude change*

Patient	*Age (y)*	*Duration of exercise (min)*	*HRmax*	*ΣR (rest)*	*ΣR (peak)*	*% Δ R*	*ST*	*Angio*
64	55	10·0	82	5·30	5·20	− 2 *	IL	Spasm
65	52	7·5	122	10·50	10·40	− 1 *	IL	Spasm
66	59	6·0	110	4·70	5·00	+ 6 *	IL	1VD
67	64	8·0	78	11·60	12·10	+ 4 *	L	1VD
68	48	7·0	135	4·55	6·05	+33 *	AIL	1VD
69	63	12·0	70	10·35	10·05	− 3 *	L	2VD
70	53	8·5	166	5·85	5·90	+ 1 *	L	2VD
71	56	9·5	104	4·80	6·05	+26 *	L	3VD
72	49	8·0	112	8·80	9·05	+ 3 *	L	3VD
73	56	10·0	135	3·65	4·70	+29 *	IL	3VD
74	54	12·0	110	4·50	7·20	+60 *	IL	3VD
75	53	5·0	118	1·40	1·65	+18 *	AIL	3VD
76	63	9·0	82	5·70	5·60	− 2 *	AIL	3VD
Mean	56	8·7	110	6·28	6·84	+13		
(SEM)	5	0·6	8	0·80	0·80	5		

For explanation to abbreviations see footnote to Table 5A.

Table 7 *Results of conventional ST analysis in this study compared to previous published reports*

Reference	*Ex*	*Electrocardiogram*	*ST*	*N*	*Sensitivity*	*Specificity*	*Predictive accuracy*	
							Positive	*Negative*
This study	T	12L	0·1	62	67%	74%	67%	74%
Weiner *et al.*[9]	T	12L	0·1	526	76%	61%	49%	86%
Barolsky *et al.*[7]	T	Orth	0·1	66	55%	95%	45%	77%
Detry *et al.*[4]	B	12L	0·1	53	88%	81%	68%	94%
			0·2	53	23%	97%	80%	73%
Reuben *et al.*[6]	T	CM5	0·1	253	47%	62%	41%	64%
Sketch *et al.*[2]	T	12L	0·1	56	45%	78%	33%	85%
Linhart *et al.*[1]	T	12L	0·1	98	71%	78%	52%	89%

Ex = Exercise test used: T, treadmill; B, bicycle.
Electrocardiogram = Electrocardiograph lead system (12L=12 lead, orth=X, Y, Z leads).
ST = Degree of ST depression used in the study in mV.

the maximum heart rate (130±8 versus 107±8, $p<0.05$). Two women showed exercise-induced hypotension without ST change during exercise and both had severe coronary disease. Five of the six women with coronary disease and no ST depression had a low peak heart rate which may, in some, account for the "abnormal" R wave response.

All 13 patients showing both ST and R wave abnormal tests had abnormalities shown on angiography, though only 11 (85%) had significant coronary stenosis (Table 6). Two showed severe unprovoked coronary spasm.

Discussion

The diagnosis of coronary artery disease in women with chest pain is difficult as even classical angina may not be diagnostic.[9] Though the poor predictive accuracy of tests in women may reflect a lower prevalence of coronary disease[8 9 20] a "positive" exercise test is associated with an increased risk for future sudden death or myocardial infarction, albeit less than that for such a result in men.[21] Previous authors have underlined the limitations of ST segment interpretation in women (Table 7). Normal angiography at rest does not necessarily relate to cardiac function at peak exercise and many patients remain symptomatic despite reassurance that all is "normal".[22]

The results of standard ST segment interpretation in this study are similar to previous work showing a test sensitivity and specificity of about 70% (Table 7). R wave analysis usefully increased predictive accuracy in many women though the results were insufficient to provide correct interpretation in all. The overall effect of combined ST and R wave analysis is to identify reliably two subgroups of women. Firstly those with a doubly negative test (no ST depression and reduced R wave amplitude at peak exercise) are most unlikely to have coronary artery disease. The only patient with such a result and abnormal coronary angiography had non-dominant right coronary disease of little clinical significance (Tables 1 and 4). Secondly the doubly positive test is highly likely to occur with coronary disease (Table 6). These two subgroups accounted for half the subjects studied.

The decrease in R wave amplitude during exercise in normal subjects has been widely reported and the phenomenon confirmed using several different electrocardiographic lead systems. The R wave decreases as heart rate increases, though the absolute change is not predictable in an individual. Of our 14 normal volunteers, 13 showed a 5% to 94% decrease from rest to peak exercise. The mechanism for R wave change is both complex and controversial and a definitive explanation has yet to be proposed, though changes in cardiac volume have been related both in theory and practice.[23–25] There is therefore a good basis for accepting reduced R wave amplitude on exercise, certainly treadmill exercise,[12–15] as a criterion for a normal test.

Increased or unchanged R wave amplitude at peak exercise is less well recognised as an index of abnormality,[26–28] though other workers have found it extremely predictive of coronary disease in men.[12–15] In this study it was only highly predictive of coronary disease if it was associated with ST segment depression (Table 6). Ischaemia may alter the QRS wave directly or produce a secondary change with increased intracardiac volume and the resultant effect in an individual will depend upon the resting electrocardiographic pattern and relative interplay of these two mechanisms. This may explain why some patients with pronounced ST depression show reduced R wave amplitude and vice versa.

Changing the percentage R wave decrease necessary to denote abnormality would alter specificity with reciprocal effect on sensitivity just as it would for ST segment change. Patients with a low heart rate response (Table 5b) often showed an unexpected increase in amplitude, perhaps reflecting increased left ventricular volume. Even if these patients are not "ischaemic" at the end of exercise the absence of a satisfactory chronotropic response represents a significant difference from the normal population.[7] Beta blockade will reduce the peak heart rate attained during an exercise test but does not of itself cause a change in the rate-R wave relation.

For women with either ST or R wave positive tests there was no reliable predictive accuracy for the presence of coronary stenosis (Tables 5a and b). Within this subgroup many showed abnormalities other than coronary disease but we stress that in this retrospective review no systematic additional studies (for example atrial pacing test) had been performed. Ergometrine was not administered to any of these women. Ellestad and colleagues[3] found only 13% of a selected group of 95 men and women with "false positive" tests to be entirely normal. In our patients seven (41%) of the 17 with "false positive" tests had abnormalities other than coronary stenosis: three had an abnormal atrial pacing test (ST depression with associated chest pain and elevation of left ventricular end-diastolic pressure), one had an abnormal left ventriculogram, one had significant mitral prolapse without regurgitation, and two had severe unprovoked coronary artery spasm unrelated to either the catheter tip or identifiable coronary disease. These abnormalities may be the underlying cause of the chest pain in the patients concerned. Indeed, by implication, patients with either abnormal ST or R wave amplitude responses and "normal" coronary arteries are more likely to have an underlying abnormality other than coronary artery stenosis. An exercise test may therefore be as accurate a diagnostic test as a coronary angiogram in women presenting with chest pain.

Of all those undergoing angiography for chest pain, 10 to 30% have ostensibly normal coronary arteries. In women, especially young women, however, as few as one-quarter have demonstrable stenoses.[8] As this study indicates that a double negative (normal ST segment and reduced R wave at peak exercise) treadmill exercise test is a good predictor for normal coronaries many women presenting with chest pain can be reassured without recourse to coronary angiography. Women with abnormal exercise tests and yet "normal" coronary angiography are a heterogeneous group, with several possible underlying aetiologies. It is this subgroup of women, in our consecutive series being about one-quarter of those investigated, that requires careful follow-up and future study if the chest pain persists.

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Requests for reprints to Dr AF Rickards, National Heart Hospital, Westmoreland Street, London W1M 8BA.

Br Heart J 1982; **48**: 169–76

Computerised cardiological case notes

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From the Department of Cardiology, St Thomas's Hospital, London

SUMMARY Optical Mark Reader forms have been used by the Cardiac Department at St Thomas's Hospital for six years to store clinical and haemodynamic data by computer. Forms are completed by clinical staff in outpatients and also for those patients undergoing cardiac catheterisation. Three documents are used to record the symptoms and signs at the clinical consultation, the results of relevant investigations, and the important findings at cardiac catheterisation. These documents are fed into a computer and data from them, together with a limited quantity of typed information, are used to produce full clinical reports for our colleagues and the case notes. These reports have saved much secretarial and medical time. A variety of analyses is available for research and management purposes.

Since the mid 1960's numerous efforts have been made to use computer methods for the routine processing of clinical data. For a variety of reasons these have not been wholly successful and, particularly in the United Kingdom, have not been widely used. Perhaps as a consequence, computer resources have been applied instead to activities more peripheral to the clinical consultation, such as patient administration, nursing and laboratory applications and, most successfully of all, to the processing of signals from complicated electronic equipment used in, for example, radiology, chemistry, nuclear medicine, and indeed cardiac catheterisation.

We believe that attempts to computerise the data obtained at a clinical consultation have been hampered by the range and quantity of the information obtainable. Many workers have solved this problem by focusing on a well defined range of disease processes to the exclusion of others: for example peptic ulcers,[1] hypertension,[2 3] and a variety of applications in which patients themselves use a computer terminal to describe their symptoms.[4] Despite reducing the problem to more manageable proportions, there still remain difficulties with the computer techniques used to record the data. Solutions usually involve either manuscript or formalised proformae (which are subsequently typed into the computer by secretarial staff) or direct use of an on-line terminal by the clinician. The former method suffers in the main from delays, transcription errors, and the need for additional staff, while the latter method involves a high capital cost, the need for doctors to acquire typing skills, and often the unacceptable time involved for each conversation.[5]

We present here a system which solves the problem of data input using Optical Mark Reader (OMR) forms on which the clinician directly records the history, physical signs, and the results of most of the more relevant investigations. The system is implemented on a medium scale time sharing computer with a typewriter terminal in the Cardiac Department and shared use of the OMR device.

The system

Three OMR forms are used, one to record the history, physical signs, electrocardiogram, chest radiograph, and echocardiographic findings, a second to record the results of more specialised investigations aimed at the diagnosis of cardiorespiratory disease, and a third to record the techniques and results of cardiac catheterisation.

PATIENT EXAMINATION OMR FORM

This document is used to record information obtained at the consultation in out-patients or on the ward and is filled in at that time by the clinician. The various sections of the form (Fig. 1) record:

—basic patient identification including hospital number

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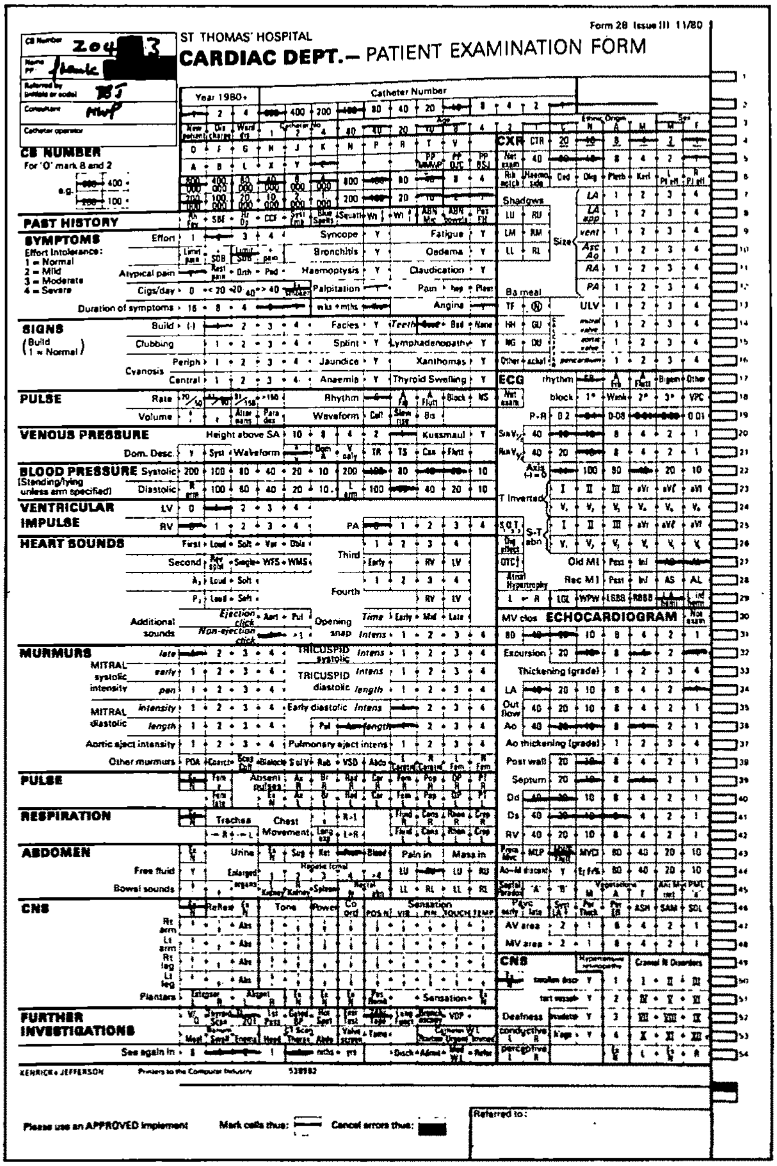
*Present address: Hammersmith Hospital, Du Cane Road, London W12.

†Present address: Norfolk and Norwich Hospital, St Stephens Road, Norwich, Norfolk.

Accepted for publication 30 March 1982



Form 28 Issue III 11/80

ST THOMAS' HOSPITAL

CARDIAC DEPT.— PATIENT EXAMINATION FORM

204 [redacted]

CS NUMBER

PAST HISTORY

SYMPTOMS

SIGNS

PULSE

VENOUS PRESSURE

BLOOD PRESSURE

VENTRICULAR IMPULSE

HEART SOUNDS

MURMURS

PULSE

RESPIRATION

ABDOMEN

CNS

FURTHER INVESTIGATIONS

CXR

ECG

ECHOCARDIOGRAM

CNS

Referred to:

Please use an APPROVED implement Mark cells thus: Cancel errors thus:

Fig. 1 *The patient examination OMR form.*

—important events in the past history

—symptoms of heart disease including effort intolerance

—the complete physical examination including auscultation

—the results of the chest *x*-ray examination

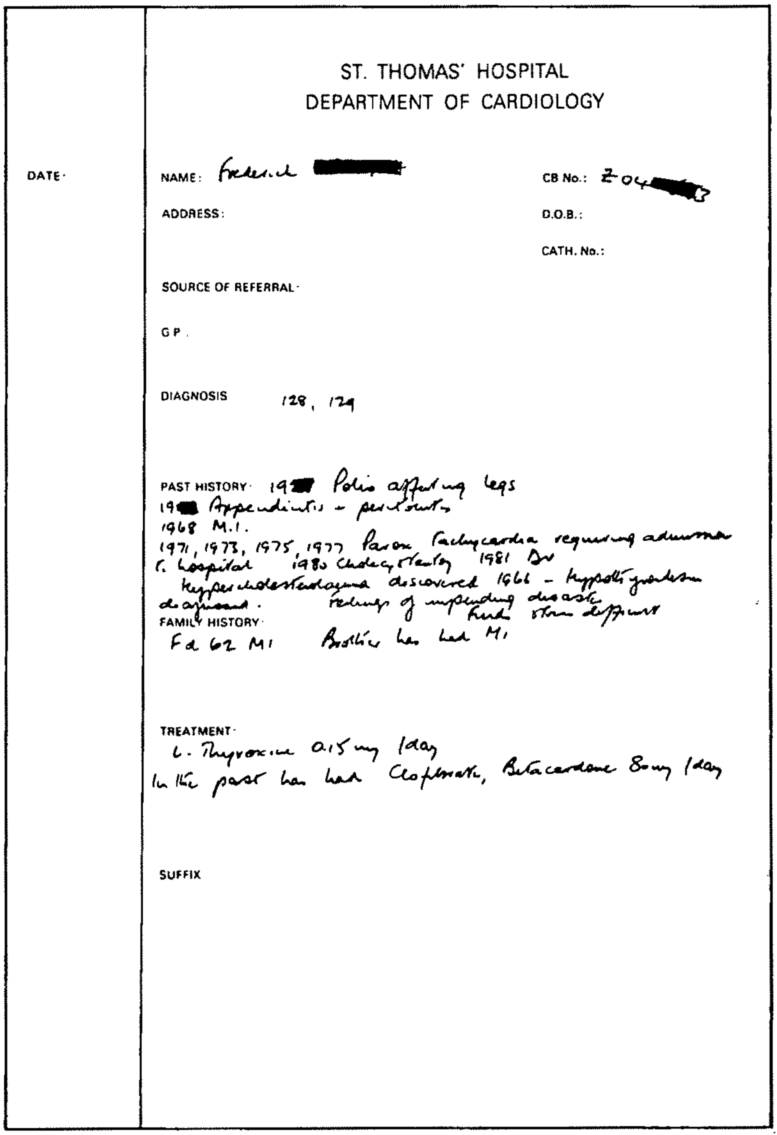
—the results of electrocardiography

—the results of echocardiography

—a list of proposed further investigations.

The clinician then records, in manuscript and on an attached sheet (Fig. 2), more comprehensive details of the past history if required, current treatment, and his diagnoses at that time. Diagnoses relevant to cardiovascular disease are numerically coded using a small, easily expandable dictionary; but non-cardiac diagnoses are recorded in text only and are therefore less amenable to subsequent analysis.

The documents are fed into the OMR by a secretary who also types in any extra information relevant to each record. If error free, the computer record is



ST. THOMAS' HOSPITAL
DEPARTMENT OF CARDIOLOGY

DATE·

NAME: Frederick [redacted]
CB No.: Z-04[redacted]
ADDRESS:
D.O.B.:
CATH. No.:
SOURCE OF REFERRAL·
G P.
DIAGNOSIS 128, 129

PAST HISTORY· 19[redacted] Polio affecting legs
19[redacted] Appendicitis – peritonitis
1968 M.I.
1971, 1973, 1975, 1977 Parox tachycardia requiring admission
c. hospital 1980 Cholecystectomy 1981 Dr
Hypercholesterolaemia discovered 1966 – hypothyroidism
diagnosed. Feelings of impending disaster
Finds stress difficult

FAMILY HISTORY·
Fa 62 MI Brother has had MI

TREATMENT·
L-Thyroxine 0.15 mg /day
In the past has had Clofibrate, Betacardone 80 mg /day

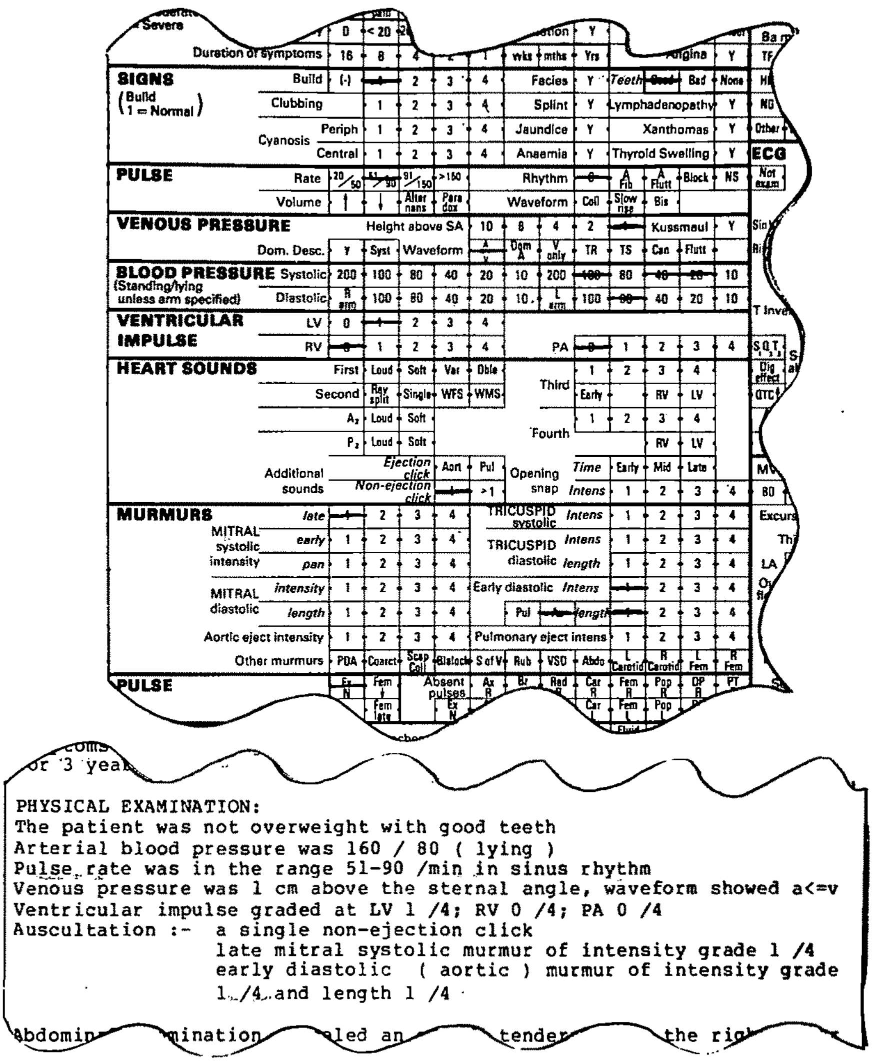
SUFFIX

Fig. 2 *The manuscript appendage to the OMR form in Fig. 1.*

added to its files, merging it with any existing information for that patient. If there are no outstanding investigations other than blood tests, a full report is then printed on the typewriter terminal in the cardiac department: this device has a typeface similar to that of an ordinary typewriter (Fig. 3). On to this report the secretaries transcribe the results of any blood tests, photocopy the finished report (Fig. 4), and distribute it to the referring clinician, the patient's general practitioner, the case notes, departmental files and, where appropriate, to our surgical colleagues.

INVESTIGATIONS OMR FORM

This document (Fig. 5) is used to record the results of more specialised investigations relevant to patients with cardiorespiratory disease. The various sections of the document include provision for recording the patient's identification including hospital number and



Severe		D	< 20						Y					
	Duration of symptoms	16	8	4	2	1	wks	mths	Yrs	gina	Y			
SIGNS	Build	(-)		2	3	4	Facies	Y	*Teeth*		Bad	None		
(Build 1 = Normal)	Clubbing		1	2	3	4	Splint	Y	Lymphadenopathy			Y		
	Cyanosis Periph		1	2	3	4	Jaundice	Y	Xanthomas			Y		
	Central		1	2	3	4	Anaemia	Y	Thyroid Swelling			Y		
PULSE	Rate	20/50		91/150	>150		Rhythm		A Fib	A Flutt	Block	NS		
	Volume	↑	↓	Alternans	Paradox		Waveform	Coll	Slow rise	Bis				
VENOUS PRESSURE	Height above SA					10	8	4	2		Kussmaul	Y		
	Dom. Desc.	Y	Syst	Waveform		A V	Dom A	V only	TR	TS	Can	Flutt		
BLOOD PRESSURE	Systolic	200	100	80	40	20	10	200	100	80	40	20	10	
(Standing/lying unless arm specified)	Diastolic	R arm	100	80	40	20	10	L arm	100	80	40	20	10	
VENTRICULAR IMPULSE	LV	0	1	2	3	4								
	RV	0	1	2	3	4	PA	0	1	2	3	4		
HEART SOUNDS	First	Loud	Soft	Var	Dble		Third	1	2	3	4			
	Second	Rev split	Single	WFS	WMS			Early		RV	LV			
	A_2	Loud	Soft				Fourth	1	2	3	4			
	P_2	Loud	Soft							RV	LV			
	Additional sounds	*Ejection click*	Aort	Pul			Opening snap *Time*	Early	Mid	Late				
		Non-ejection click	1	>1			*Intens*	1	2	3	4			
MURMURS	MITRAL systolic intensity *late*	1	2	3	4		TRICUSPID systolic *Intens*	1	2	3	4			
	early	1	2	3	4		TRICUSPID diastolic *Intens*	1	2	3	4			
	pan	1	2	3	4		*length*	1	2	3	4			
	MITRAL diastolic *intensity*	1	2	3	4		Early diastolic *Intens*	1	2	3	4			
	length	1	2	3	4		Pul *length*	1	2	3	4			
	Aortic eject intensity	1	2	3	4		Pulmonary eject intens	1	2	3	4			
	Other murmurs	PDA	Coarct	Scap Coll	Blalock	S of V	Rub	VSD	Abdo	L Carotid	R Carotid	L Fem	R Fem	
PULSE		Ex N	Fem ↓	Absent pulses	Ax R	Br	Rad	Car R	Fem R	Pop R	DP R	PT		
			Fem late	Ex N				Car L	Fem L	Pop L				

```
 oms
r 3 yea

PHYSICAL EXAMINATION:
The patient was not overweight with good teeth
Arterial blood pressure was 160 / 80 ( lying )
Pulse rate was in the range 51-90 /min in sinus rhythm
Venous pressure was 1 cm above the sternal angle, waveform showed a<=v
Ventricular impulse graded at LV 1 /4; RV 0 /4; PA 0 /4
Auscultation :-  a single non-ejection click
                 late mitral systolic murmur of intensity grade 1 /4
                 early diastolic  ( aortic ) murmur of intensity grade
                 1 /4 and length 1 /4

Abdomin    ination    led an    tende    the ri
```

Fig. 3 *A section of the computer produced clinical report together with that part of the OMR form from which it was generated.*

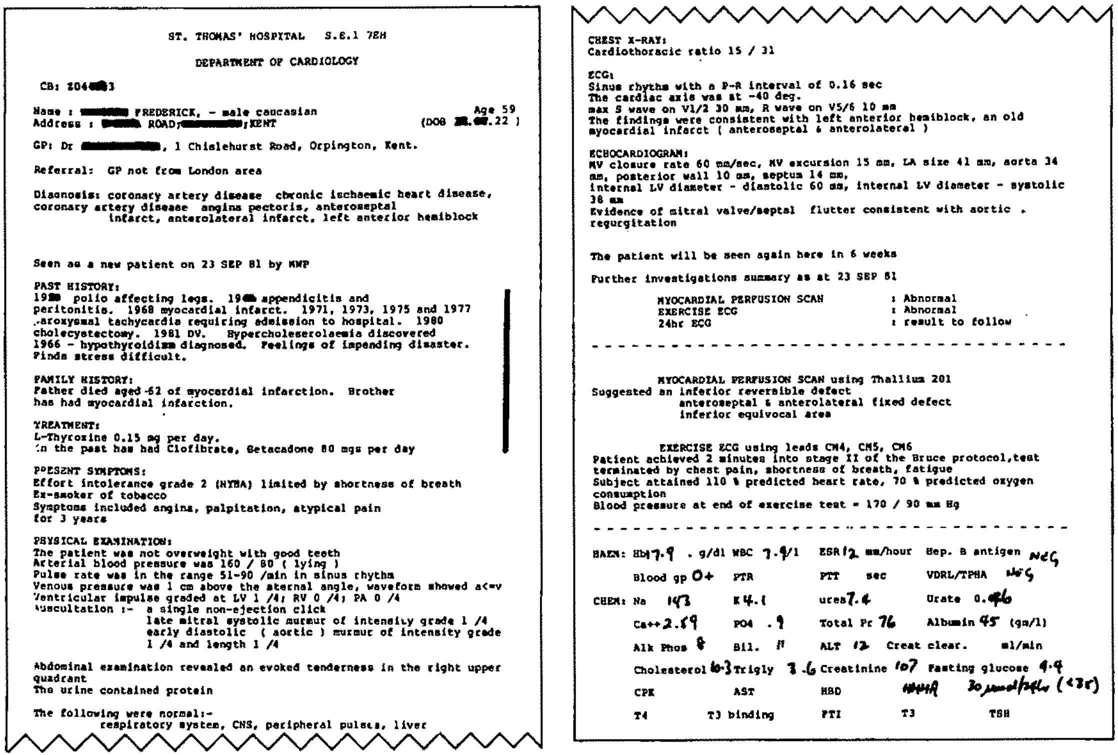
the results of:

- —lung function tests including patch testing and blood gas estimations
- —24 hour ambulatory electrocardiographic monitoring
- —exercise testing
- —venous occlusion plethysmography
- —myocardial perfusion scans (201Tl)
- —hot spot (pyrophosphate) scans
- —first pass isotope perfusion studies
- —gated blood pool studies
- —ventilation/perfusion lung scans.

Most of the above investigations are performed by staff closely involved with the cardiac department and they complete the OMR forms instead of issuing formal reports. Lung function tests are done elsewhere, however, and our technical and secretarial staff transcribe these results on to the OMR form. The documents are then fed into the computer as described above, save that no free text information is necessary. This input is merged with any existing information and a complete, cumulative report printed in the cardiac department.

CATHETER OMR FORM

This document is attached to the manuscript catheter record and is a summary of its contents. It allows the following to be recorded:



```
                    ST. THOMAS' HOSPITAL   S.E.1 7EH

                       DEPARTMENT OF CARDIOLOGY

 CB: 104[redacted]3

Name : [redacted] FREDERICK, - male caucasian                    Age 59
Address : [redacted] ROAD;[redacted];KENT                    (DOB [redacted].[redacted].22 )

GP: Dr [redacted], 1 Chislehurst Road, Orpington, Kent.

Referral:  GP not from London area

Diagnosis: coronary artery disease  chronic ischaemic heart disease,
coronary artery disease  angina pectoris, anteroseptal
           infarct, anterolateral infarct, left anterior hemiblock


Seen as a new patient on 23 SEP 81 by MMP

PAST HISTORY:
19[redacted]  polio affecting legs.  19[redacted] appendicitis and
peritonitis.  1968 myocardial infarct.  1971, 1973, 1975 and 1977
Paroxysmal tachycardia requiring admission to hospital.  1980
cholecystectomy.  1981 DV.   Hypercholeserolaemia discovered
1966 - hypothyroidism diagnosed.  Feelings of impending disaster.
Finds stress difficult.

FAMILY HISTORY:
Father died aged 62 of myocardial infarction.  Brother
has had myocardial infarction.

TREATMENT:
L-Thyroxine 0.15 mg per day.
In the past has had Clofibrate, Betacadone 80 mgs per day

PRESENT SYMPTOMS:
Effort intolerance grade 2 (NYHA) limited by shortness of breath
Ex-smoker of tobacco
Symptoms included angina, palpitation, atypical pain
for 3 years

PHYSICAL EXAMINATION:
The patient was not overweight with good teeth
Arterial blood pressure was 160 / 80 ( lying )
Pulse rate was in the range 51-90 /min in sinus rhythm
Venous pressure was 1 cm above the sternal angle, waveform showed a<=v
Ventricular impulse graded at LV 1 /4; RV 0 /4; PA 0 /4
Auscultation :-  a single non-ejection click
                 late mitral systolic murmur of intensity grade 1 /4
                 early diastolic  ( aortic ) murmur of intensity grade
                 1 /4 and length 1 /4

Abdominal examination revealed an evoked tenderness in the right upper
quadrant
The urine contained protein

The following were normal:-
          respiratory system, CNS, peripheral pulses, liver
```

Continued above right

```
CHEST X-RAY:
Cardiothoracic ratio 15 / 31

ECG:
Sinus rhythm with a P-R interval of 0.16 sec
The cardiac axis was at -40 deg.
max S wave on V1/2 30 mm, R wave on V5/6 10 mm
The findings were consistent with left anterior hemiblock, an old
myocardial infarct ( anteroseptal & anterolateral )

ECHOCARDIOGRAM:
MV closure rate 60 mm/sec, MV excursion 15 mm, LA size 41 mm, aorta 34
mm, posterior wall 10 mm, septum 14 mm,
internal LV diameter - diastolic 60 mm, internal LV diameter - systolic
38 mm
Evidence of mitral valve/septal  flutter consistent with aortic .
regurgitation


The patient will be seen again here in 6 weeks

Further investigations summary as at 23 SEP 81

          MYOCARDIAL PERFUSION SCAN            : Abnormal
          EXERCISE ECG                         : Abnormal
          24hr ECG                             : result to follow

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -


          MYOCARDIAL PERFUSION SCAN using Thallium 201
Suggested an inferior reversible defect
             anteroseptal & anterolateral fixed defect
             inferior equivocal area


          EXERCISE ECG using leads CM4, CM5, CM6
Patient achieved 2 minutes into stage II of the Bruce protocol,test
terminated by chest pain, shortness of breath, fatigue
Subject attained 110 % predicted heart rate, 70 % predicted oxygen
consumption
Blood pressure at end of exercise test = 170 / 90 mm Hg

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

HAEM: Hb17.9 . g/dl WBC 7.9/l    ESR12 mm/hour  Hep. B antigen NEG

      Blood gp O+   PTR          PTT    sec     VDRL/TPHA  NEG

CHEM: Na  143       K4.1         urea7.4        Urate  0.46

      Ca++2.59      PO4  .9      Total Pr 76    Albumin 45  (gm/l)

      Alk Phos 8    Bil.  11     ALT 12  Creat clear.    ml/min

      Cholesterol 10.3Trigly  3.6 Creatinine 107 Fasting glucose 4.9

      CPK           AST          HBD          [illegible]   30 [illegible] (<31)

      T4        T3 binding       FTI          T3           TSH
```

Fig. 4 *The clinical report. The bar at the right margin indicates the proportion derived from free text data.*

- —patient identification
- —arterial and venous catheters used and their site of entry
- —investigative procedures employed
- —complications of catheterisation
- —diagnoses, 70 of which may be marked but others may be coded and keyed in
- —angiographic findings
- —a summary of the haemodynamic indices.

The marking of this form is partly done by technical staff during the procedure and completed by clinical staff after the angiographic and other data have been analysed. The OMR forms are then fed in by secretaries who also key in any extra diagnoses or complications which could not be marked on the form. A brief report is produced by the computer but this is used only to check the data and is then discarded.

Analysis facilities

The most useful output derived from the patient examination and investigations OMR forms is the clinical report: these data and that from the catheter OMR form, however, may also be analysed to produce various tabulations which help the department perform more effectively. Several analyses are available of which the most important are an audit, a breakdown of costs, and an extract facility.

AUDIT

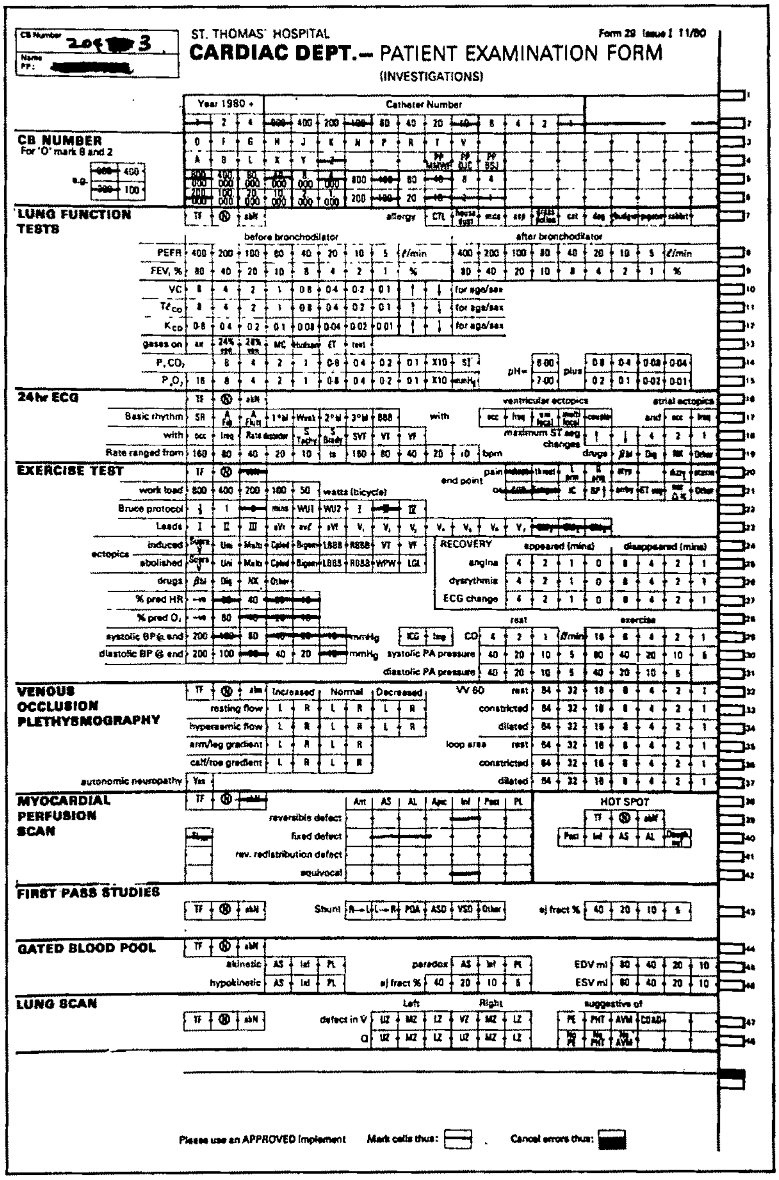
This examines all catheterisations within a stated interval and lists the catheters used, entry sites, and procedures employed against the incidence of complications. This information is used to prepare the annual catheter laboratory report and to review complication rates associated with each technique.

COSTS

The computer automatically accumulates the cost of each catheterisation by individually costing the various types of catheter used, the angiogram(s), and procedure(s). These costs may be listed by operator, time, and source of referral; the output is prepared overnight after the request has been entered on the terminal in the cardiac department.

EXTRACT

This is the most important analysis facility available on the system. It enables the rapid identification of all



ST. THOMAS' HOSPITAL

CARDIAC DEPT.— PATIENT EXAMINATION FORM

(INVESTIGATIONS)

Form 29 Issue I 11/80

CB NUMBER

LUNG FUNCTION TESTS

24hr ECG

EXERCISE TEST

VENOUS OCCLUSION PLETHYSMOGRAPHY

MYOCARDIAL PERFUSION SCAN

FIRST PASS STUDIES

GATED BLOOD POOL

LUNG SCAN

Please use an APPROVED implement Mark cells thus: Cancel errors thus:

Fig. 5 *The investigations OMR form.*

records that share any defined characteristic; it is used mainly for research. The research worker enters details into the computer using the terminal and, after a short delay, obtains a list of the identities of all records that satisfy his requirements. He would normally then use this list to gain access to the case notes or any other records and proceed by conventional means. The most frequent need is for a list of all patients in a given diagnostic category; this can be done using a single scan of the data on the computer. It is possible to manipulate several scans so as to satisfy more sophisticated requirements involving logically linked series of criteria. The process of extraction occurs during the conversation between researcher, using a keyboard, and the computer. The system can also subsequently produce a complete print out of all selected records.

Other analyses include listings of diagnosis frequency and a breakdown of workload by consultant and referral source. The record linkage capability of the system may be used to perform longitudinal studies on any defined variable, for example effort intolerance, blood pressure.

Development

The system was developed with eight months of analyst and programmer effort over a seven year period since 1974. A further three weeks were spent by clinical staff defining their requirements and assessing the results. The computer programmes were written in FORTRAN IV using soft ware originally developed for the microbiology system at St Thomas's.[6] Considerable effort was invested in the design of this soft ware to ensure that changes to the system, and in particular to the number and design of both OMR forms and reports, could be made with the minimum of effort and delay.[7] Many changes can be made without any reprogramming. The computer holds 4500 catheter records going back to 1973 and 5000 examination records since 1976, 1500 of which relate to outpatients. The investigations OMR form has only recently been added to the system and as yet only 250 documents have been fed in. A total of 50 OMR forms are entered each week.

Results

The system is operated entirely by the staff of the cardiac department who readily absorbed its routine operation into their daily work. The marking of OMR forms was unexpectedly easy and rapid. The patient examination form was the most time-consuming and takes approximately 10 minutes to complete, but so did the previous task of dictation which it replaced. To mark each investigation and catheter OMR form is a trivial task and takes at most a few minutes. To enter the 50 OMR forms into the computer takes 40 minutes each week, of which 30 are spent commuting to and from the microbiology laboratory where the OMR device is located. To annotate the records takes a weekly total of two-and-a-half hours of secretarial time, most of which is spent typing in free text. Each report takes two minutes to print, but since it is done by the unattended operation of the computer terminal, no further secretarial time is involved. The addition of laboratory results, photocopying, and distribution are all tasks unchanged from the previous system. The time spent by technical and clinical staff in running the system thus shows no significant change from previous methods. Each week our secretarial staff take some three-and-a-half hours to process 50 documents. This compares very favourably with the equivalent time of 25 hours previously spent typing the dictated letters.

The savings effected by the various analyses and listings produced by the computer are more difficult to quantify. The annual catheter laboratory report used to take a doctor 10 days to prepare, most of which was spent on the manual assembly of analysis sheets. The audit facility has reduced this to one day actually writing the report. The costing figures prove extremely useful in convincing the administration not only that the department cares about cost but also that cardiac investigations are not as expensive as it thought! The extract facility was, and with increasing frequency continues to be, used to identify groups of patients for teaching or research purposes. Examples of the ways in which the system helps our research activities include:

—a review of the electromagnetic flow probe[8]
—factors determining angina in aortic stenosis[9]
—the results of endomyocardial biopsy studies in mitral leaflet prolapse[10]
—visual complications of mitral leaflet prolapse.[11]

To identify all patients in these categories would have meant checking by hand all the manuscript catheter records, a prohibitively time-consuming and boring task; using the computer it was done in minutes rather than months.

Our problems lie mainly in the shared use of the OMR device and the unreliability of the central computer. Commuting to and from the microbiology laboratory accounts for much of the time spent entering OMR forms and is particularly tiresome when errors require forms to be re-entered. The obvious solution for this (a second OMR) was impractical because of the high cost (£11 000) of the reading devices. Unreliability of both mark reader and central computer is a problem but seldom causes more than minor inconvenience. Our system was designed so as to tolerate unavailability of the computer for up to two days continuously and this limit has only been exceeded on two occasions in six years. There is a small but continuing requirement for retrospective manipulation of the files by our computer department. Inappropriate marking of the OMR forms by new clinical staff is a recurrent minor irritation but this soon responds to correction and encouragement from our secretaries.

Discussion

There is little doubt that computers can be of great value in the production of management and research statistics if, and only if, they can be used to record accurate and complete information economically. In many cases the computer may also help the routine operation of a clinical or paraclinical department. The production of analytical forms of output presents no major computer programming or organisational problems. The major difficulty in clinical work is recording the patient data and this we believe can be overcome given a recording technique appropriate to the data involved, and a computer system of sufficient flexibility and reliability. The system we describe achieves during its routine operation a net saving of 22 hours of secretarial time per week and provides a management and research tool of great power and utility. Furthermore, it has been implemented with virtually no opposition from those who use it. We ascribe this firstly to the OMR techniques used, secondly to the flexibility of the computer programs, and thirdly to the careful avoidance of any duplication of work, however temporary, during the transition from manual to automated methods. The system was therefore seen from the outset to be easy to use, easy to modify, and to involve less and not more work for those concerned with its day to day operation.

Reliability and local control of development would be improved by the use of a mini- or microcomputer dedicated to our department, particularly if it formed part of a network linked to other applications. Such an arrangement would also provide much needed insurance against failure.

We have not been able wholly to computerise our clinical record. Much of the text which is currently typed in, and merely reproduced verbatim on our clinical reports, could well be supplied by interaction with other computer applications participating in a network. Thus treatment details could be supplied by a pharmacy application, the past history from a diagnostic system with record linkage capability, and the laboratory results included automatically rather than transcribed as at present. Despite this, a clinical report must be complete and we do not therefore foresee a time when free text can be completely eliminated from our system.

Design of suitable OMR forms would permit similar applications in other fields such as insurance medical examinations, industrial health, and the health records of the armed forces. For such purposes these forms would not only allow for the easy storage, retrieval, and analysis of large quantities of data but would also encourage the uniform recording of clinical information by different clinicians. Whether or not doctors in other specialities would find the method suitable would depend on the computer facilities to which they had access, the nature and extent of the information they wish to record, and the determination and enthusiasm that they, and the computer staff they employ, apply to the problem. While cardiology undoubtedly forms but a subset of general medicine, we believe that it is not such a super speciality that our results are not applicable elsewhere.

Unless medical computing can be seen to work in the routine clinical environment to the satisfaction of clinical and ancillary staff, and of a cost conscious and sceptical administration, then there is a danger that computer professionals will increasingly regard it as difficult and unrewarding and that clinicians will continue to view computer systems as expensive, time-consuming, and unproductive gimmicks.

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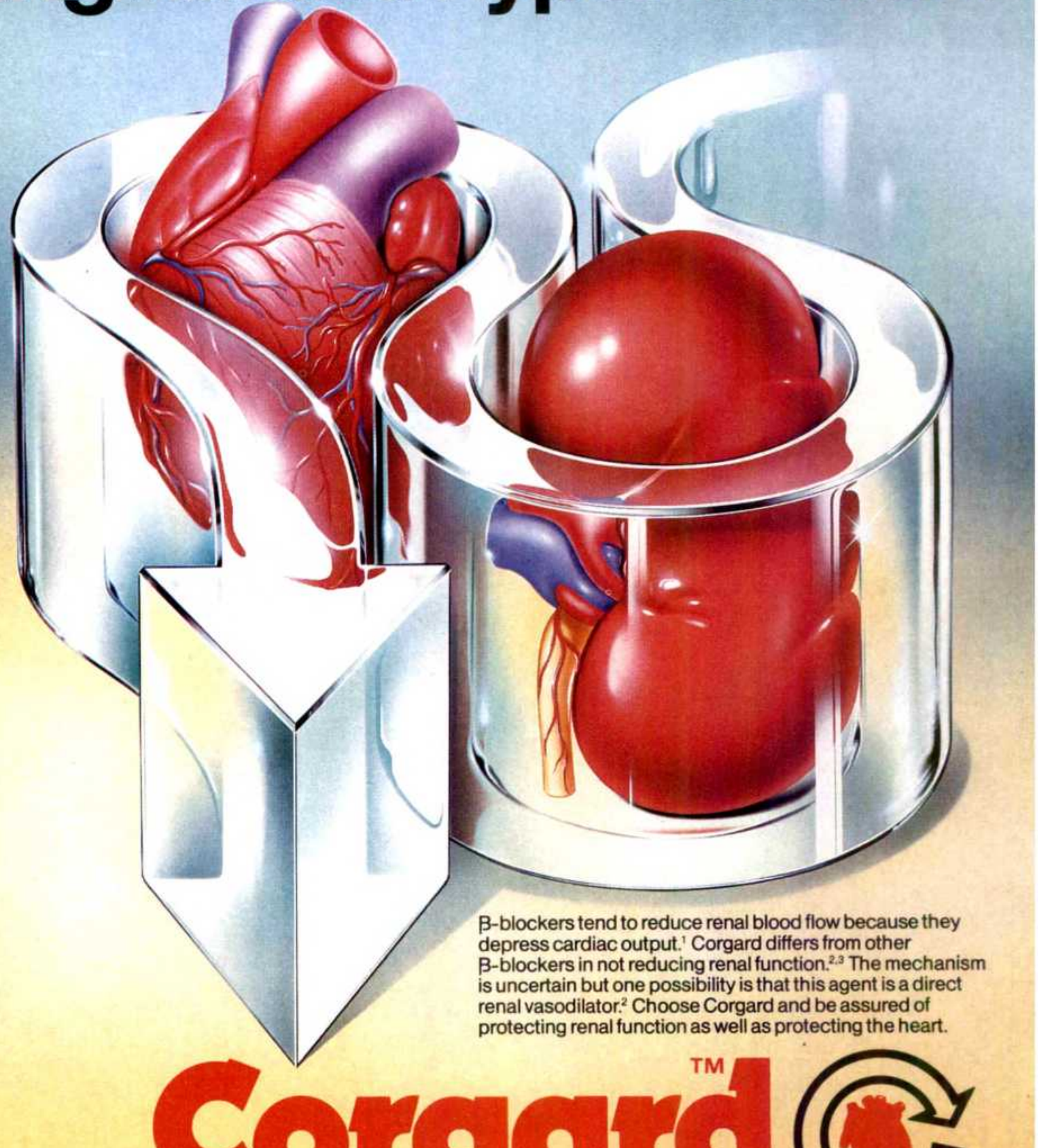

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Br Heart J 1982; **48**: 177–9

Large calcified right atrial myxoma in a newborn
Rare cause of neonatal death

SINDA B DIANZUMBA, GURENDRA CHAR

From the Departments of Medicine (Cardiology) and Pathology, University Hospital of the West Indies, Kingston, Jamaica

SUMMARY A newborn baby girl presented at birth with severe cyanosis, congestive cardiac failure, and an ischaemic leg ulcer, and died within 10 hours of birth. Necropsy disclosed a large haemorrhagic, calcified right atrial myxoma obstructing the tricuspid valve.

Right atrial myxoma is a rare cause of heart failure in infancy and childhood.[1-4] Since its clinical diagnosis is elusive in this age group,[4] it is usually not suspected in the differential diagnosis of cyanotic neonates with congestive cardiac failure. The implications, however, of making the diagnosis of this potentially curable tumour during life are obvious. We report a newborn baby with a calcified right atrial myxoma simulating cyanotic congenital heart disease.

Case report

A 19 year old primigravida was admitted to the University Hospital of the West Indies maternity ward with severe pre-eclampsia and hydramnios at 30th week of pregnancy. Her blood group was A, Rh positive. Four weeks after admission, fetography was normal. Eight weeks later spontaneous rupture of the membranes occurred. She was transferred to the labour ward for induction and thirty hours later a female child, weighing 3025 g, was born. The baby was cyanotic and had generalised oedema with a bloated abdomen. She had no spontaneous cry. Respirations were forced and gasping in type. Since no resuscitative measures were undertaken, the baby died 10 hours after delivery. The placenta was large, oedematous, and fragmented. Necropsy showed that the lungs and liver were congested and the right atrium and ventricle were enlarged. There was a large glistening, pedunculated tumour (measuring $2 \times 2 \times 1 \cdot 8$ cm) attached to the endocardium of the posterior wall of the right atrium (Fig. 1), completely obstructing the tricuspid valve orifice. Its surface was haemorrhagic and ulcerated. The cut sections of the tumour showed multiple areas of haemorrhages and calcification. Histology and special stains confirmed the tumour to be a myxoma (Fig. 2). There was a moderate amount of ascitic fluid in the abdomen and

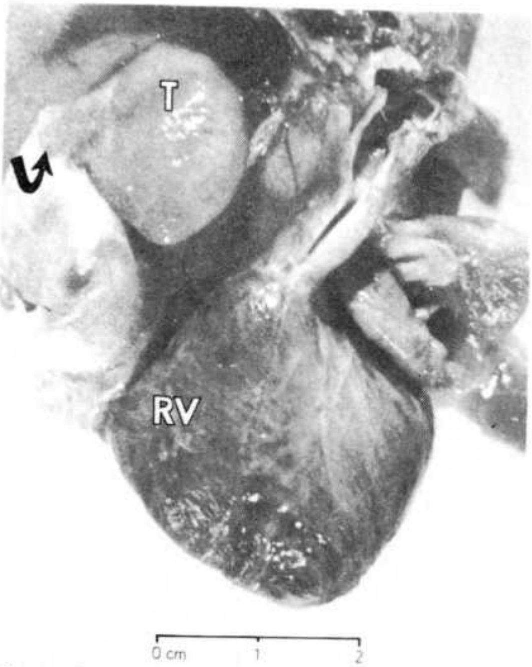

Fig. 1 *Gross specimen of the heart depicting the tumour (T) within a dilated opened right atrium, arising from the endocardium of the posterior atrial wall. The arrow points to the pedicle of the tumour on the endocardial surface. RV, unopened right ventricle.*

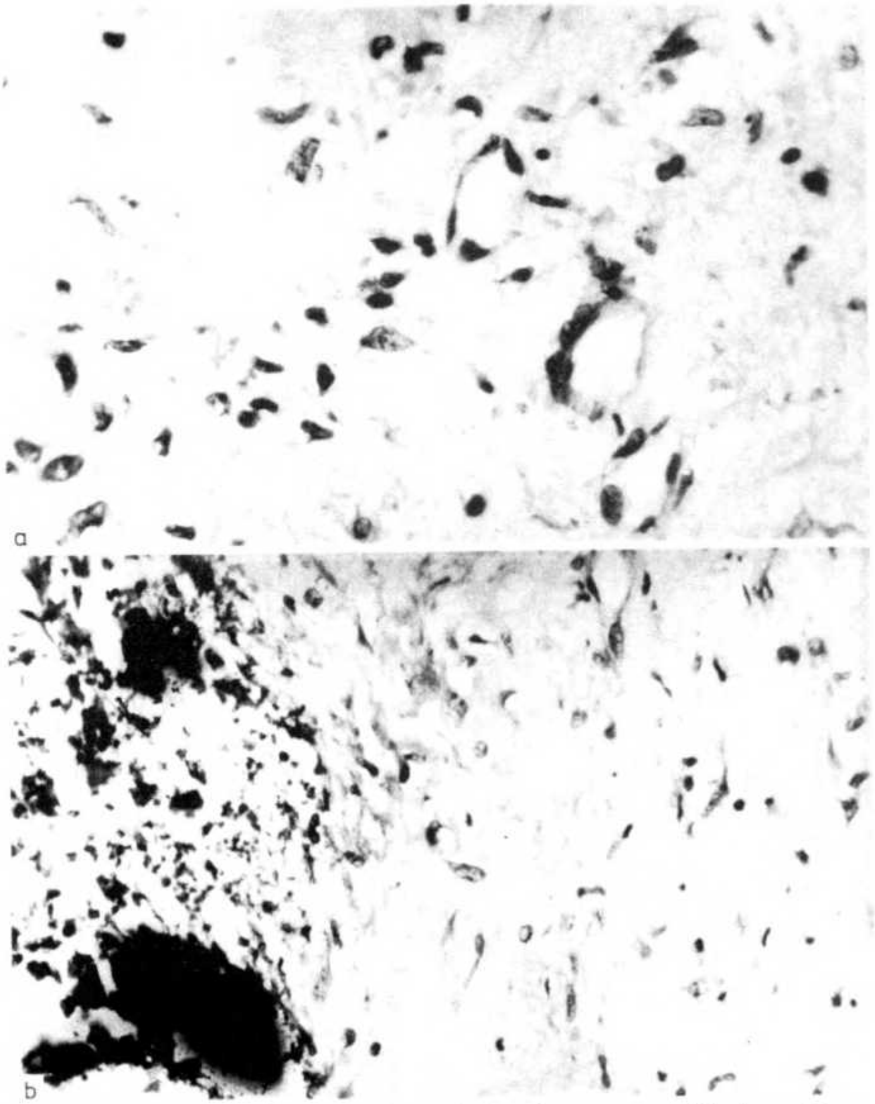

Fig. 2 *(a) Histology of the myxoma showing pseudo-glandular arrangement of the characteristic lepidic cells within polysaccharide rich stroma. (H and E. Original magnification × 560.) (b) Photomicrograph of myxoma showing calcification (dark deposits on the left side). (H and E. Original magnification × 350.)*

an ischaemic ulcer of the left foot was also noted. The latter was thought to be a result of a paradoxical embolus which appeared to have occurred in utero.

Comments

A right atrial myxoma, like the commoner left atrial myxoma, usually causes symptoms and signs of obstruction.[5] Our patient is the youngest reported presenting with a calcified tumour. At birth she showed cyanosis, congestive cardiac failure, anasarca, as well as an ischaemic ulcer on her leg, presumably the result of paradoxical systemic embolus through a patent foramen ovale. Unfortunately she did not live long enough to undergo appropriate investigation.

This presentation emphasises the fact that right atrial myxoma can be a rare cause of fatal neonatal cyanotic heart failure. The tumour was extremely large relative to the baby's heart size and undoubtedly produced severe obstruction to right ventricular filling, leading to a low cardiac output and severe right heart failure. The mild hypertrophy of the right ventricle which was present also suggests associated tricuspid regurgitation, which is found with calcified right atrial myxoma.[3] With modern diagnostic methods and improved surgical techniques, this lesion may be successfully treated if the diagnosis is suspected.[3-5] Cardiac tumours such as atrial myxomas are now readily diagnosed by M-mode echocardiography and particularly two dimensional real time echocardiography where movement, shape, and location can be clearly defined in relation with cardiac structures.[6-9] Unfortunately this newborn baby was not referred to a cardiologist.

Thus, the unusual features of this case are the age of the baby, the right atrial location of the myxoma, calcification of the myxoma in utero, the large size of the tumour with obstructive signs presenting as severe cyanotic congenital heart disease at birth, probable paradoxical systemic embolisation present at birth, and an apparent extremely rapid growth of the myxoma in utero.

We thank Professor Vasil Persaud, Department of Pathology, for reviewing the slides of the myxoma.

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Br Heart J 1982; **48**: 180–3

Unusual vascular ring in infant with pulmonary atresia and ventricular septal defect

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SUMMARY A 3-day-old infant investigated for cyanotic heart disease was found to have partial DiGeorge syndrome and pulmonary atresia with ventricular septal defect. The only source of pulmonary blood flow was a right-sided persistent ductus arteriosus which originated from an aberrant right subclavian artery. Such a vascular ring has not been described previously. Surgical treatment included a left-sided prosthetic shunt in infancy followed by resection of the ligamentum arteriosum and right subclavian artery during the second year of life.

A left aortic arch with aberrant right subclavian artery and right ductus arteriosus is a rare form of complete vascular ring. Only cases in which there was also a retro-oesophageal and right descending thoracic aorta, with the ductus arising from the dorsal aortic root, have been recorded in the English publications.[1 2] The patient presented here is unique in that the descending aorta was on the left and the persistent ductus arteriosus originated from the aberrant subclavian artery itself. The association of this anomaly with pulmonary atresia, ventricular septal defect, and partial DiGeorge syndrome created special problems in surgical management.

Case report

A male infant, 3·2 kg, was transferred at 3 days of age for investigation of increasing cyanosis. Pregnancy and delivery had been uncomplicated, and he first became "dusky" with tachypnoea seven hours after birth. On physical examination, the baby had odd facies, with pointed ears, widely spaced eyes, and down-turned mouth. Moderate central cyanosis, a soft systolic murmur along the left sternal edge, and a single second heart sound were noted. No murmur was heard along the right sternal edge. Relevant laboratory investigations included an arterial Po_2 of 32 mmHg in room air, a serum calcium of 1·58 nmol/l, and the absence of thymic shadow on chest *x*-ray film.

Cardiac catheterisation showed pulmonary atresia with a ventricular septal defect, left aortic arch, and an aberrant right subclavian artery. The sole blood supply to the lungs came from a right-sided persistent ductus arteriosus arising from the aberrant subclavian artery (Fig. 1a). With patency of the ductus maintained by an infusion of prostaglandin E_1 at 0·1 μg/kg per min, a modified Blalock-Taussig shunt[3] was constructed the following day, using a 6 mm Gore-Tex conduit between the left subclavian and left pulmonary arteries. Postoperative recovery was haemodynamically satisfactory but complicated by multiple episodes of twitching, necrotising enterocolitis, and monilia infection. Investigation of the patient's hypocalcaemia subsequently disclosed low levels of parathormone on three occasions (70–140 ng/l; normal=130–380 ng/l). Thymic dependent lymphocytes, however, were present and appeared to have normal function. A diagnosis of partial DiGeorge syndrome[4] was made, and the child was eventually dismissed from hospital at 3 months of age. Mild congestive heart failure was controlled by digoxin, and serum calcium levels maintained by dihydrotachysterol. The latter was discontinued after one year without recurrence of hypocalcaemia.

A poor feeder throughout infancy, the baby suffered progressive dysphagia and was unable to take solid food at 14 months of age. Reinvestigation of his cardiovascular status at that time showed that the ductus arteriosus had closed and the shunt was patent (Fig. 1b). Systemic arterial saturation was 74%. On barium swallow, the oesophagus was compressed laterally and posteriorly, consistent with a vascular ring formed by the left aortic arch, aberrant right subclavian artery, and the right ligamentum arteriosum (Fig. 2). The patient subsequently underwent division of the ligamentum arteriosum and aberrant right subclavian artery through a right thoracotomy with

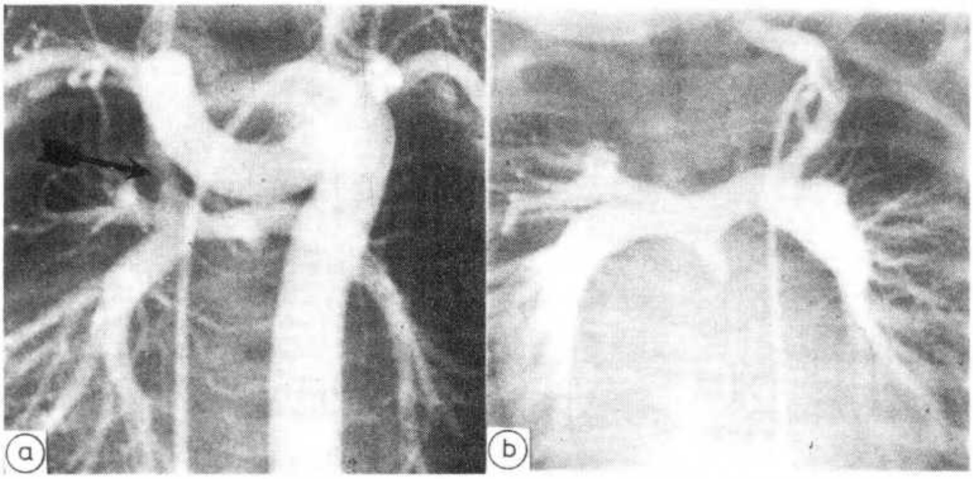

Fig. 1 *Aortogram at 3 days of age (a) and selective injection into the origin of the left subclavian artery 14 months later (b). The catheter shows the position of the ascending aorta in the first investigation, with contrast opacifying the distal arch, the aberrant right subclavian artery, and the descending aorta. Confluent pulmonary arteries are supplied by a right-sided persistent ductus arteriosus which is stenosed at its mid-portion (arrow).*

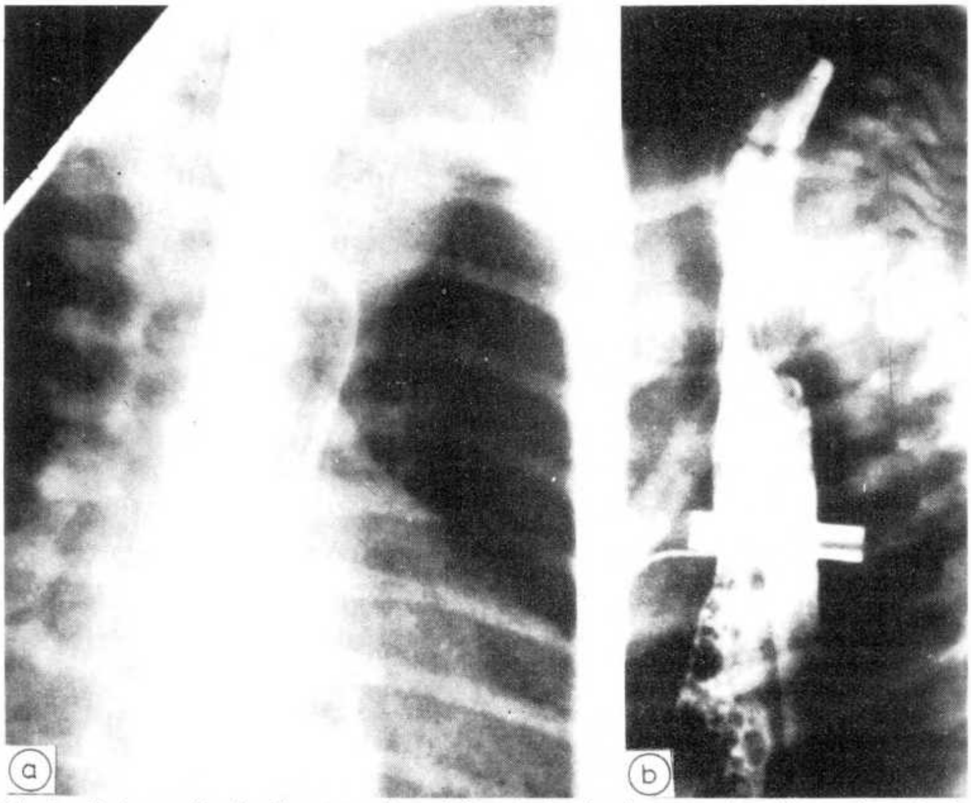

Fig. 2. *Barium swallow in oblique (a) and lateral (b) projections showing compression of the oesophagus by the vascular ring.*

complete relief of his feeding problems. At 3½ years of age, he now awaits correction of his pulmonary atresia and ventricular septal defect.

Discussion

Anomalies of the aortic arch are encountered not infrequently in palliative surgery for cyanotic congenital heart disease. Among 841 patients explored with a view to systemic-pulmonary anastamosis, Bahnson and Blalock observed 40 vascular rings, including 36 instances of retro-oesophageal subclavian artery.[5] The aberrant subclavian artery on either side can be used to perform a satisfactory Blalock-Taussig anastomosis, and the resulting complete vascular ring has not caused symptoms of tracheal or oesophageal compression.[6 7] When the anomaly is a double aortic arch, using the smaller arch for the shunt achieves simultaneous palliation of cyanosis and division of the vascular ring.[8 9] In our patient, however, the pulmonary blood supply depended upon the integrity of the vascular ring, and the presence of a right-sided ductus precluded a Blalock-Taussig shunt on the side opposite to the aortic arch. With knowledge of the arch anatomy from preoperative angiography, it was possible to plan the initial prosthetic shunt on the side of the aortic arch, and this permitted subsequent interruption of the vascular ring when it became symptomatic.

Embryologically, this anomaly can be explained by persistence of the right sixth arch as the ductus arteriosus and the right eighth dorsal aortic root as the aberrant subclavian artery, with regression of the left sixth arch and the right fourth arch.[10] Factors that determine the side of the descending aorta are unknown but, it is of interest in this case, where the aorta remained on the left, that the retro-oesophageal portion of the subclavian artery was considerably larger than normal (Fig. 1a). Since the patient also had pulmonary atresia, it seems unlikely that the large segment resulted from preferential blood flow during development. Developmental anomalies of the third and fourth pharyngeal pouches are often associated with those of aortic arch derivatives, but this is thought to represent a response to a common teratogenic factor rather than a causal relation.[11]

The likelihood of compression symptoms occurring from this vascular anomaly is difficult to estimate. Among 14 patients reported with left aortic arch, right descending aorta, and right ligamentum arteriosum half suffered respiratory distress or feeding problems in infancy.[12 13] Associated cardiac anomalies were common, but none required palliative surgery, and the vascular ring was treated on its own merits.[2 14] In each case, the ligamentum or ductus arteriosus was divided through a right thoracotomy rather than through the left-sided exposure used for most vascular rings.

Congenital heart disease as a presentation of the DiGeorge syndrome is well recognised and should be suspected in any infant with craniofacial stigmata and anomalies of the aortic arch.[11 15] The twitching episodes caused by hypocalcaemia in this patient were of little consequence; but sudden death during cardiac catheterisation or after correction of acidosis with alkali has been attributed to arrhythmias secondary to exacerbated hypocalcaemia.[4] In the partial DiGeorge syndrome, patients may have considerable cell-mediated immunity and, despite profound hypocalcaemia in infancy, achieve remission permanently during early childhood. Since survival of such patients has now been seen into the third decade,[16] aggressive treatment of the cardiovascular anomalies appears to be justified.

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Br Heart J 1982; **48**: 184–8

Permanent right bundle-branch block heralded by intermittent block and ventricular extrasystoles

A 13-year observation

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SUMMARY A patient is described in whom the occurrence of frequent ventricular extrasystoles of right ventricular origin and intermittent right bundle-branch block caused by interpolation of these extrasystoles heralded the slow development of permanent right bundle-branch block over a period of observation of 13 years. Such a clinical course suggested gradual progression of an organic lesion in the intraventricular conducting system. The differential diagnosis of intermittent bundle-branch block and aberrant intraventricular conduction, and possible mechanisms of ectopic impulse formation in the presence of bundle-branch block are discussed.

The dependence of intermittent and transient bundle-branch block on heart rate changes is well known,[1–3] with the tachycardia-dependent variety more commonly seen than the bradycardia-dependent variety. The former is caused usually by sinus acceleration and rarely by other mechanisms. In contrast to aberrant conduction of supraventricular premature systoles, intermittent and transient bundle-branch blocks are thought to reflect pathological changes in the intraventricular conducting system,[1–3] but few reports have documented their transition to permanent bundle-branch block. In this communication, we report a case of intermittent right bundle-branch block caused by interpolated ventricular extrasystoles, which slowly progressed to right bundle-branch block over 13 years of observation.

Case report

A 70-year-old man was admitted to the Izu-Nirayama Hot Spring Hospital on 25 October 1966, for rehabilitation of a left hemiplegia resulting from an attack of cerebral thrombosis seven months earlier. He had no speech disturbance, was able to stand up using crutches, but was unable to walk. Cardiological examination was unremarkable except for a prominent aortic knuckle on the chest *x*-ray film. He was discharged in April 1967, but re-entered the hospital in August 1967 for further rehabilitation where he remained until May 1980, when he was transferred to another hospital for the treatment of a bladder tumour. While in hospital his blood pressure was 140 to 180/70 to 90 mmHg. Serum electrolytes were normal and blood urea nitrogen fluctuated between 5·7 and 10·7 mmol/l (16 and 30 mg/100 ml). His cholesterol level was 6·5 to 7·8 mmol/l (250 to 300 mg/100 ml) in the early years in hospital, with subsequent drop to 4·7 to 6·2 mmol/l (180 to 240 mg/100 ml). He never experienced anginal pain or congestive failure.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram on his first admission showed normal sinus rhythm at a rate of 65/min, with a PR interval of 0·16 s and a QRS duration of 0·06 s. The QRS complex in lead I showed an R pattern, and the frontal QRS axis was +45°. No signs of ventricular hypertrophy or ischaemia were noted. In April 1967, an Rs pattern appeared in lead I, with slight QRS widening (0·08 s) and a change in the axis to +20°. The QRS morphology in lead I changed back to R in March 1968, to Rs in November 1968, and again to R in December 1968. An rsR′ pattern was never observed in lead V1 during this period. ST-T abnormalities suggesting slight anterolateral wall ischaemia gradually developed in late 1968. On 11 December 1968, he developed a fever of 39·3°C, with symptoms of acute bronchitis. An associated sinus tachycardia of 130/min did not significantly alter intraventricular conduction. After January 1969, sinus bradycardia prevailed. When his rate rose transiently to 80/min on

18 November 1969, QRS duration was increased to 0·10 s, and incomplete right bundle-branch block was diagnosed for the first time, with an rsR′ pattern in V1. Thereafter, sinus bradycardia again persisted with normal intraventricular conduction.

During October 1972, several atrial extrasystoles appeared with aberration of right bundle-branch block type. In July 1974, an interpolated ventricular extrasystole was first observed, its left bundle-branch block configuration suggesting a right ventricular origin.[4] [5] The following sinus beat had a prolonged PR interval, but a normal QRS. Electrocardiograms obtained in September and October showed similar ventricular extrasystoles with full compensatory pauses. When another interpolated extrasystole occurred in November 1974, the next sinus beat showed a right bundle-branch block configuration (Fig. 1A). From this month to May 1975, repeated electrocardiograms almost always showed ventricular extrasystoles. Whenever they were interpolated, the following sinus beat showed right bundle-branch block, whereas no QRS changes occurred after extrasystoles with compensatory pauses. On 20 June 1975, for the first time right bundle-branch block was present during sinus rhythm (60/min), with only the sinus beat following a compensatory pause showing a normal QRS (Fig. 1B). During the next two years, sinus beats showed either a normal QRS or right bundle-branch block—transient right bundle-branch block. When intraventricular conduction was normal during this period, an interpolated ventricular extrasystole was followed by one to seven sinus beats showing right bundle-branch block. On 27 February 1976, the sinus beats in leads I, II, III, aVR, aVL,

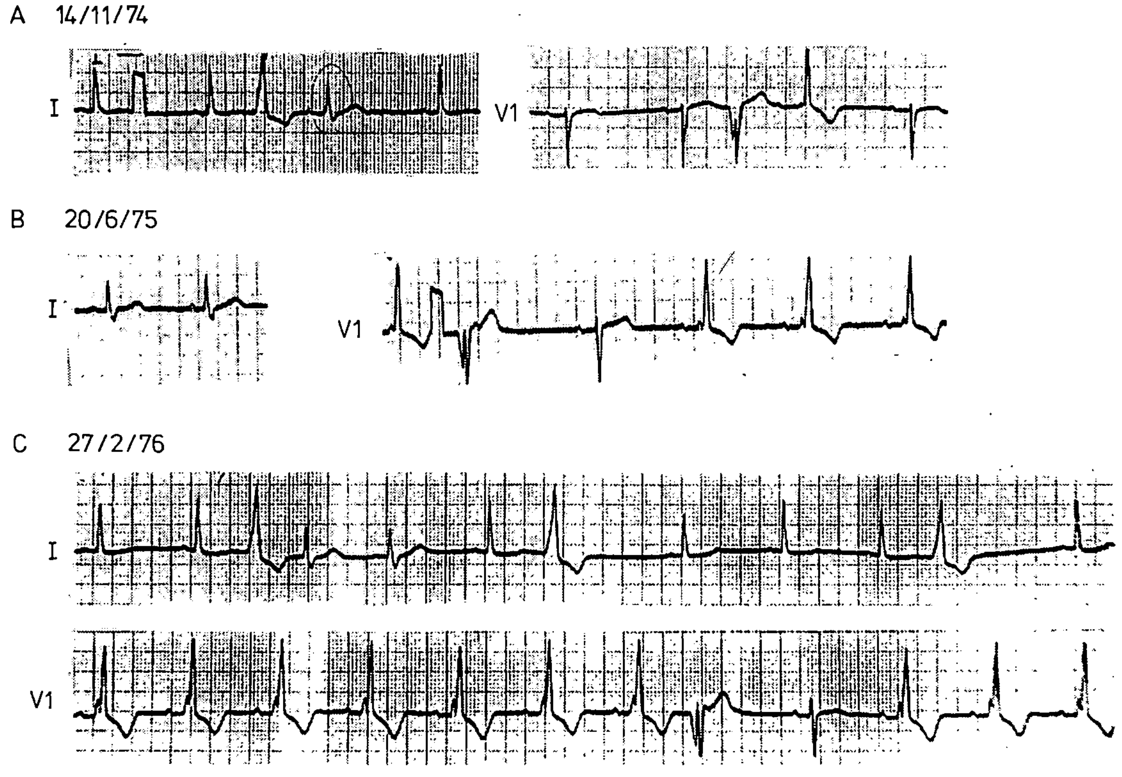

Fig. 1 *In (A) (14/11/74), an interpolated ventricular extrasystole (beat 3 in both leads I and V1) caused the appearance of a right bundle-branch block configuration in the following sinus beat. In (B) (20/6/75), a right bundle-branch block pattern persisted during sinus rhythm, whereas the sinus beat terminating the compensatory pause (beat 3 in V1) after a ventricular extrasystole showed restoration of a normal QRS. In (C) (27/2/76), most sinus beats showed normal intraventricular conduction in lead I, where an interpolated ventricular extrasystole (beat 3) caused the appearance of right bundle-branch block in two subsequent sinus beats. Extrasystoles with compensatory pauses (beats 7 and 11) did not affect the following sinus QRS. In lead V1, right bundle-branch block persisted, and a ventricular extrasystole with a compensatory pause (beat 8) returned the QRS of the following sinus beat to normal. The sinus rate was slightly faster in V1 as compared with I. Note the almost identical QRS configuration of all the extrasystoles, with a left bundle-branch block pattern.*

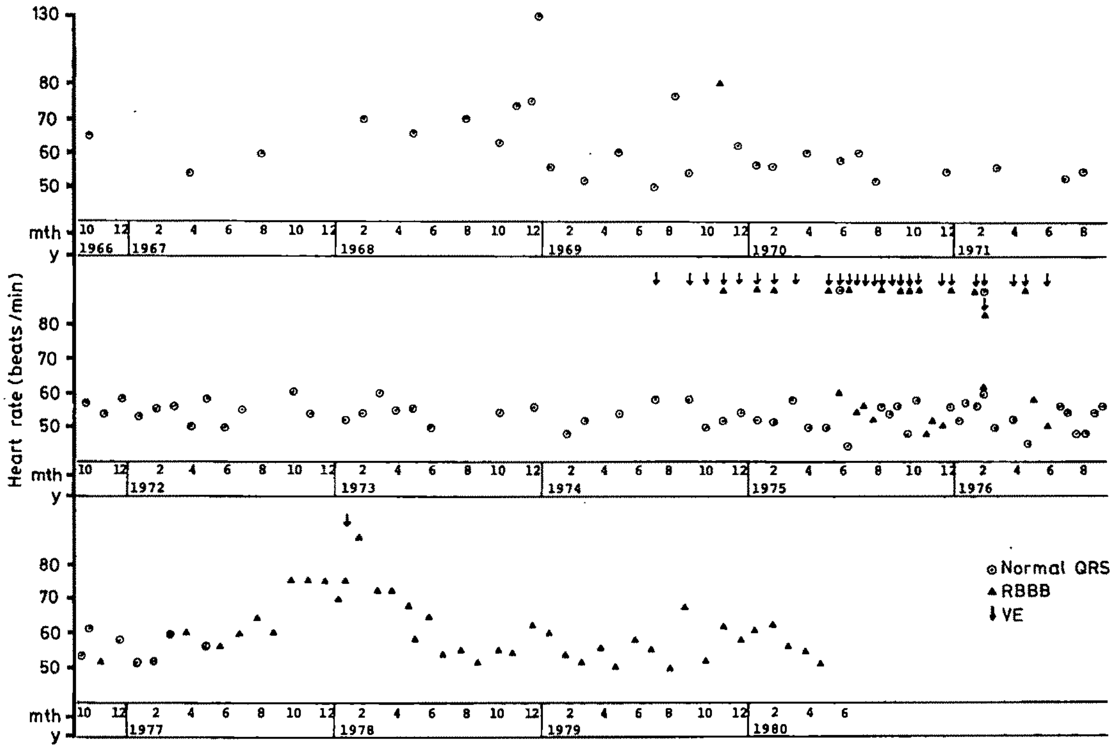

Fig. 2 *Heart rate and intraventricular conduction in all the electrocardiograms recorded during the 13 years. mth, month; y, year; VE, ventricular extrasystoles. A solid triangle under an arrow indicates the appearance of right bundle-branch block in sinus beat(s) following an interpolated extrasystole. An open circle under an arrow shows restoration of a normal QRS pattern in sinus beats following a ventricular extrasystole with a compensatory pause. Those arrows unaccompanied by symbols indicate either extrasystoles with a compensatory pause in the presence of normal intraventricular conduction or interpolated extrasystoles in the presence of right bundle-branch block in sinus rhythm, so that no alterations in QRS of the following sinus beats occurred. Note the continuous extrasystolic activity from July 1974 to June 1976. The increased heart rates between October 1977 and June 1978 were caused by a slightly higher body temperature after a fracture of the femur. Persistence of right bundle-branch block after re-establishment of sinus bradycardia suggests permanent blockage of the bundle.*

aVF, and V4, V5, V6 had a normal QRS, and interpolated ventricular extrasystoles produced right bundle-branch block in several following sinus beats, whereas an extrasystole with a compensatory pause in the presence of right bundle-branch block in leads V1, V2, and V3 restored the QRS to normal in one sinus beat (Fig. 1C).

From July 1976, these ventricular extrasystoles almost completely disappeared, and sinus beats occasionally showed transient right bundle-branch block. Finally, right bundle-branch block became permanent in June 1977, with all tracings in the subsequent three years showing this morphology. Fig. 2 summarises the entire course of these electrocardiographic abnormalities.

Discussion

The first noteworthy observation in this case is that the intermittent right bundle-branch block was caused by interpolated ventricular extrasystoles and not by the usual acceleration of sinus rhythm.[1-3] To the authors' knowledge, only one similar case has previously been reported.[3] When the QRS of a supraventricular beat becomes abnormal upon a significant shortening of the cycle length, however, aberrant conduction must be differentiated. Based on earlier observations on aberrant conduction of atrial extrasystoles,[6] Watanabe and Nishimura[7] proposed that the appearance of a bundle-branch block pattern in a supraventricular beat occurring later than the preceding U wave would favour the diagnosis of intermittent bundle-branch block. This is based on the premise that aberrant conduction results from physiological refractoriness of the intraventricular conducting system, whereas tachycardia-dependent bundle-branch block is caused by an abnormally prolonged refractory period in a damaged bundle-branch.[8] Though the above criterion is thus arbitrary, its application to Fig. 1 suggests intermittent right bundle-branch block as the likely diagnosis.

Second, in the present case, a slow progressive development of right bundle-branch block was documented by continuous observation. The various stages included, first, the appearance of a right bundle-branch block pattern in one (to seven) sinus beat(s) following an interpolated ventricular extrasystole, secondly the restoration of a normal sinus QRS after an extrasystole with a compensatory pause in the presence of right bundle-branch block, and thirdly persistence of right bundle-branch block in all sinus beats regardless of the heart rate. Such a clinical course suggests progression of an organic lesion involving the right bundle-branch system. It is interesting to ask how long it took for the conduction disturbance to mature into permanent block. If the appearance of the right bundle-branch block pattern in the sinus beat after an interpolated ventricular extrasystole in November 1974 is considered the first sign of abnormal intraventricular conduction, two and a half years elapsed before the right bundle-branch block became permanent in June 1977. Conversely, if we assume that certain pathological changes in the right bundle-branch were already present in November 1969, when acceleration of sinus rhythm was associated with transient, incomplete right bundle-branch block, the process took more than seven and a half years. Since repeated electrocardiographic recordings during the intervening five years never showed sinus rates faster than 62/min, and since the first interpolated extrasystole in July 1974 did not alter the following sinus QRS, it is difficult to determine which of the above two calculations is more accurate. Furthermore, it may be questioned whether the waxing and waning of the small s wave in lead I, beginning in April 1967, indicated a mild conduction disturbance in the right bundle-branch.

The third peculiarity in the present case is that extrasystoles of right ventricular origin occurred frequently when the right bundle-branch block was intermittent or transient, whereas they disappeared entirely after the block became permanent. Watanabe *et al.*[5] earlier reported that, in the presence of intraventricular conduction disorders, the incidence of ventricular extrasystoles was significantly increased and that those extrasystoles tended to arise from the areas of the blocked bundle or fascicle. These observations suggested a close relation between the conduction disturbance and ectopic impulse formation, and hence, the role of re-entry in the genesis of extrasystoles. One may speculate, therefore, that in our present case, areas of unidirectional block and slow conduction were present in the Purkinje system at the time conduction in the right bundle-branch was still unstable.

With reference to the occurrence of intermittent bundle-branch block associated with ventricular extrasystoles, Castellanos *et al.*[9] reported a case of pseudo-left bundle-branch block produced by a concealed premature beat. In their case, an ectopic impulse arising in the left bundle-branch apparently depolarised only part of this bundle, left refractory tissue, and blocked the conduction of the next sinus impulse therein. Conversely, as the ectopic impulse of right ventricular origin in our case produced a manifest QRS, the impulse must have depolarised the entire ventricular mass, and probably the left bundle-branch system as well (perhaps in a retrograde fashion). These two cases would thus carry different implications. The case reported by Tokunaga *et al.*[3] is also different from ours, as the interpolated ventricular extrasystole had a right bundle-branch configuration (suggesting a left ventricular origin), which caused the appearance of right bundle-branch block in the following sinus beat. Here, the right bundle-branch may be the last tissue to be depolarised by, and to repolarise after, the extrasystole, thus readily blocking the sinus impulse which closely follows the extrasystole even when the refractory period in this bundle is not abnormally prolonged.

Addendum

After this paper was submitted for publication, it was learned that the patient died of renal failure resulting from a cancer of the urinary bladder, and associated left heart failure, in June 1981. All his electrocardiograms during the last 13 months showed persistence of right bundle-branch block.

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Br Heart J 1982; **48**: 189–91

Severe subpulmonary obstruction caused by an aneurysmal tissue tag complicating an infundibular perimembranous ventricular septal defect

M BONVICINI, G PIOVACCARI, F M PICCHIO

From Istituto di Malattie dell'Apparato Cardiovascolare dell'Università degli Studi di Bologna, Italy

SUMMARY A case of severe right ventricular obstruction caused by a huge aneurysmal tissue tag is described associated with a perimembranous ventricular septal defect with an infundibular extension.

Angiograms and surgical inspection clearly showed that the ventricular septal defect extended into the outlet septum. The distinctive feature of this case was the severity of the gradient related to the peculiar position of the aneurysmal tissue in the outlet portion of the ventricle.

We presume that such an aneurysm, however small it is, developing in association with a ventricular septal defect with an infundibular extension may be a potential cause of severe obstruction and should therefore be carefully followed in the ensuing years.

Aneurysms of the membranous septum, consisting of a fibrous tissue tag, are commonly found in patients with a ventricular septal defect and their appearance usually precedes a diminution or even spontaneous closure of the ventricular septal defect.[1 2] Right ventricular outflow tract obstruction, usually not very severe, is one of the rare complications described in association with an aneurysm of the membranous septum.

The purpose of this communication is to present a case of a huge fibrous tissue tag associated with a perimembranous ventricular septal defect extending into the infundibular region and causing severe right ventricular outflow tract obstruction, which was observed 26 years after the first cardiac catheterisation.

Case report

A 36-year-old man known to have a heart murmur from the age of 6 months underwent cardiac catheterisation with angiocardiography at 13 years of age (1957), which showed a gradient of 30 mmHg between the right ventricle and pulmonary artery, but no left-to-right shunt at ventricular level. At right ventriculography a subpulmonary diaphragm was suspected. No left sided angiography was performed. At 31 years of age cardiac catheterisation was again performed because of increased right ventricular hypertrophy on the electrocardiographic examination, which showed a "transvalvular" gradient of 80 mmHg. A diagnosis of pulmonary stenosis was made, and the patient refused cardiac surgery.

Five years later he was sent to our institution because of the appearance of exertional dyspnoea. On examination the following signs were found: an "a" wave on the jugular pulse, a systolic thrill at the left sternal border, and a grade 4/6 pansystolic murmur with a crescendo/decrescendo configuration.

The electrocardiogram showed severe right ventricular hypertrophy with strain. A gradient of 105 mmHg across the outflow tract of the right ventricle without any left-to-right shunt was shown at cardiac catheterisation.

Right and left ventricular injections showed a huge septal aneurysm bulging into the right ventricular outflow tract (Fig. 1). Post-stenotic dilatation of the pulmonary infundibulum was also found. During surgery the right ventricle and the infundibular septum were seen to be hypertrophic, but the free anterior wall of the infundibulum was thin and dilated. There was a huge fibrous tissue tag anterior and superior to the anteroseptal leaflet of the tricuspid valve (Fig. 2). Two small defects were found at the apex of the aneurysm. An incision made between these two defects showed a perimembranous ventricular septal defect with an infundibular extension, 1·5 cm in diameter.

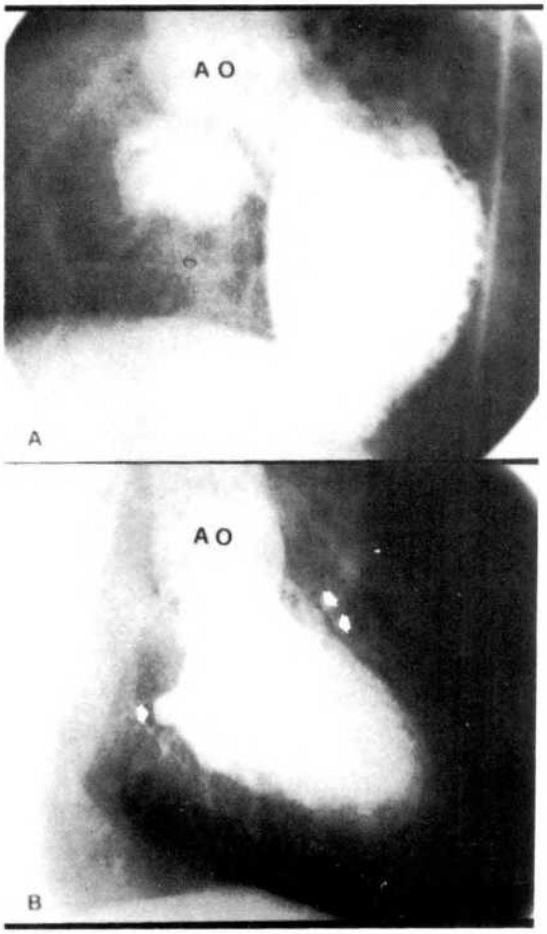

Fig. 1 *Left ventricular injection in long axial projection (A) and right anterior oblique (B). A huge aneurysmal tissue tag bulges into the right ventricular outflow tract (double arrows). A prolapse of the posterior leaflet of the mitral valve (single arrow) is also present.*

The ventricular septal defect was closed by suturing a "teflon" patch at the muscular base of the defect, thus reinforcing the extra aneurysmal tissue. An outflow patch was also placed. The peak systolic pressure in the right ventricle and pulmonary artery was 35 mmHg at the end of this procedure.

Discussion

It is well known that a ventricular septal defect in the membranous septal area may be reduced or even closed by a frequently associated fibrous tissue tag resulting from fibrin proliferation and/or an adhesion of tricuspid valve tissue to the edges of the defect.[1–4] Bacterial endocarditis, intracavity thrombus formation with systemic emboli, conduction and rhythm disturbances, tricuspid regurgitation, and right ventricular outflow tract obstruction are rare complications of an aneurysm of the membranous septum.[1–5]

Although every perimembranous ventricular septal defect can develop an aneurysm, this event is more frequently found in the ones that extend into the inlet or trabecular septum because of their proximity to the tricuspid septal leaflet.

The diagnosis of an aneurysm of the membranous septum can be detected by using elongated angiographic projections of the left ventricle,[6] but now it can also be diagnosed by the use of two dimensional echocardiography.[7]

A prolapsed aortic valve leaflet in a supracristal ventricular septal defect, however, has echocardiographic appearances similar to those of an aneurysm of the membranous septum and should therefore be carefully ruled out.[8]

In our case the ventricular septal defect, as recently proposed,[6] can be classified as perimembranous, extending into the infundibulum. In these particular types of defect the interventricular portion of the membranous septum is deficient and the defect extends anteriorly towards the infundibular septum.

It is easy to understand how an aneurysmal tissue tag which occludes an infundibular perimembranous ventricular septal defect can cause right ventricular outflow obstruction, quite possibly severe, if, as we have shown, the aneurysmal dimension is large.

The patient we have described shows how the development and severity of right ventricular outflow obstruction can be the result of a progressive growth of aneurysmal tissue in this peculiar position. Having reviewed the reported cases of an aneurysm of the membranous septum associated with right ventricular outflow tract obstruction, we suspect that the perimembranous ventricular septal defect had an infundibular extension, at least in the majority of these cases.

In a case previously reported[9] of a 12-year-old patient, the gradient was 20 mmHg, which was approximately the same as the gradient found in the first haemodynamic study of our patient at a similar age. In another observation,[10] the infundibular gradient was 60 mmHg whereas in the second study of our case the gradient was 80 mmHg (the ages of both cases were again similar). This, we believe, supports our hypothesis that the obstruction not only develops from an associated infundibular hypertrophy but also from the increase in the size of the aneurysm.

In conclusion, we think that every time a transinfundibular gradient, however small it may be, is recorded in a ventricular septal defect with an aneurysm of the membranous septum, the existence of a perimembranous defect with an infundibular exten-

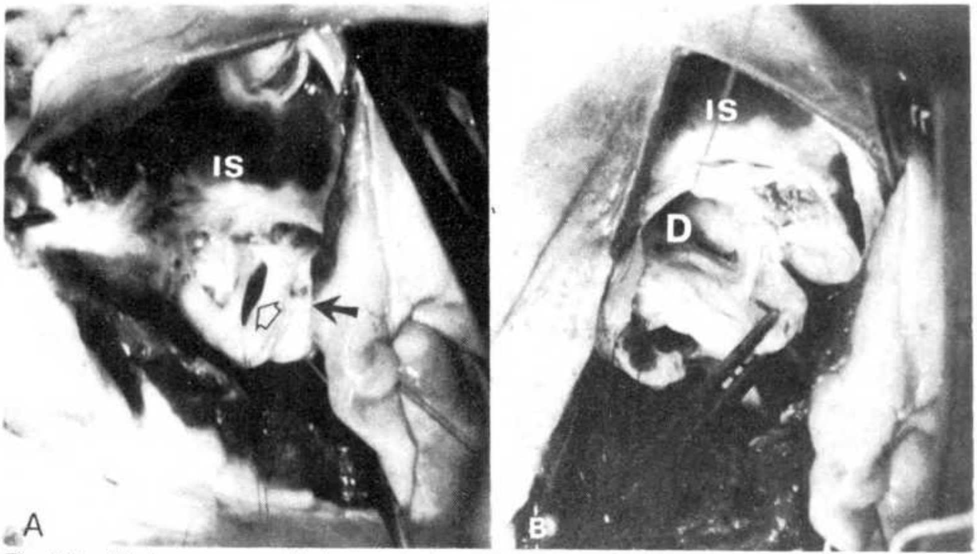

Fig. 2(A) *The huge aneurysm (black arrow) is situated below the infundibular septum (IS). One of the small defects in the aneurysm is evident (open arrow). (B) After the incision of the aneurysm a perimembranous ventricular septal defect (D) with infundibular extension appears.*

sion should be suspected. If, either with the use of elongated angiographic projections or with two dimensional echocardiography, this suspicion is confirmed, we think that these patients should be carefully followed for the possible development of right ventricular outflow tract obstruction.

We wish to thank Professor A Pierangeli and Dr P Mikus of the Cattedra di Chirurgia del Cuore e dei Grossi Vasi dell'Università di Bologna who performed the operation on this patient.

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Notices

Br Heart J 1982; **48**: 192

British Cardiac Society

The Autumn Meeting will take place at Wembley on 6 and 7 December 1982 and the closing date for receipt of abstracts is 11 August 1982.

The Annual General Meeting for 1983 will take place in Bristol on 12 and 13 April, and the closing date for abstracts will be 4 January 1983.

The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts will be 28 July 1983.

International conference on cardiac arrest and resuscitation

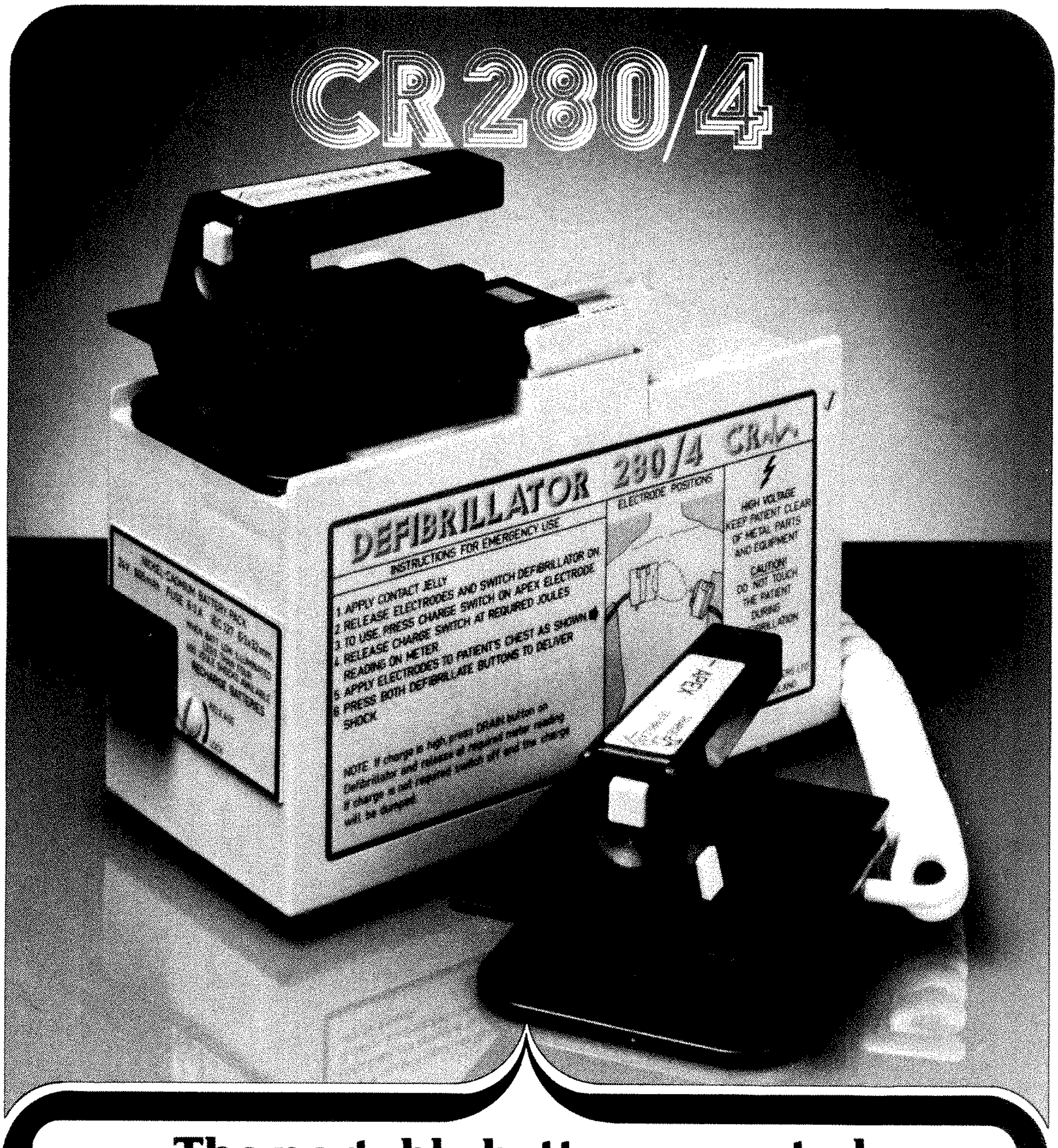
This conference, sponsored by the British Heart Foundation in association with the Community Resuscitation Advisory Council, BASICS, and the Royal Postgraduate Medical School, Hammersmith, will be held in Brighton on 19 to 21 October 1982. Inquiries to: Conference Services Limited, 3 Bute Street, London SW7 3EY.

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

Erratum

The authors (Bainton *et al*) regret that in redrafting their summary (*Br Heart J* 1982; 47: 483) the second line of the fifth paragraph had ". . . serum ***high*** density lipoprotein cholesterol". This should have read "serum *low* density lipoprotein cholesterol".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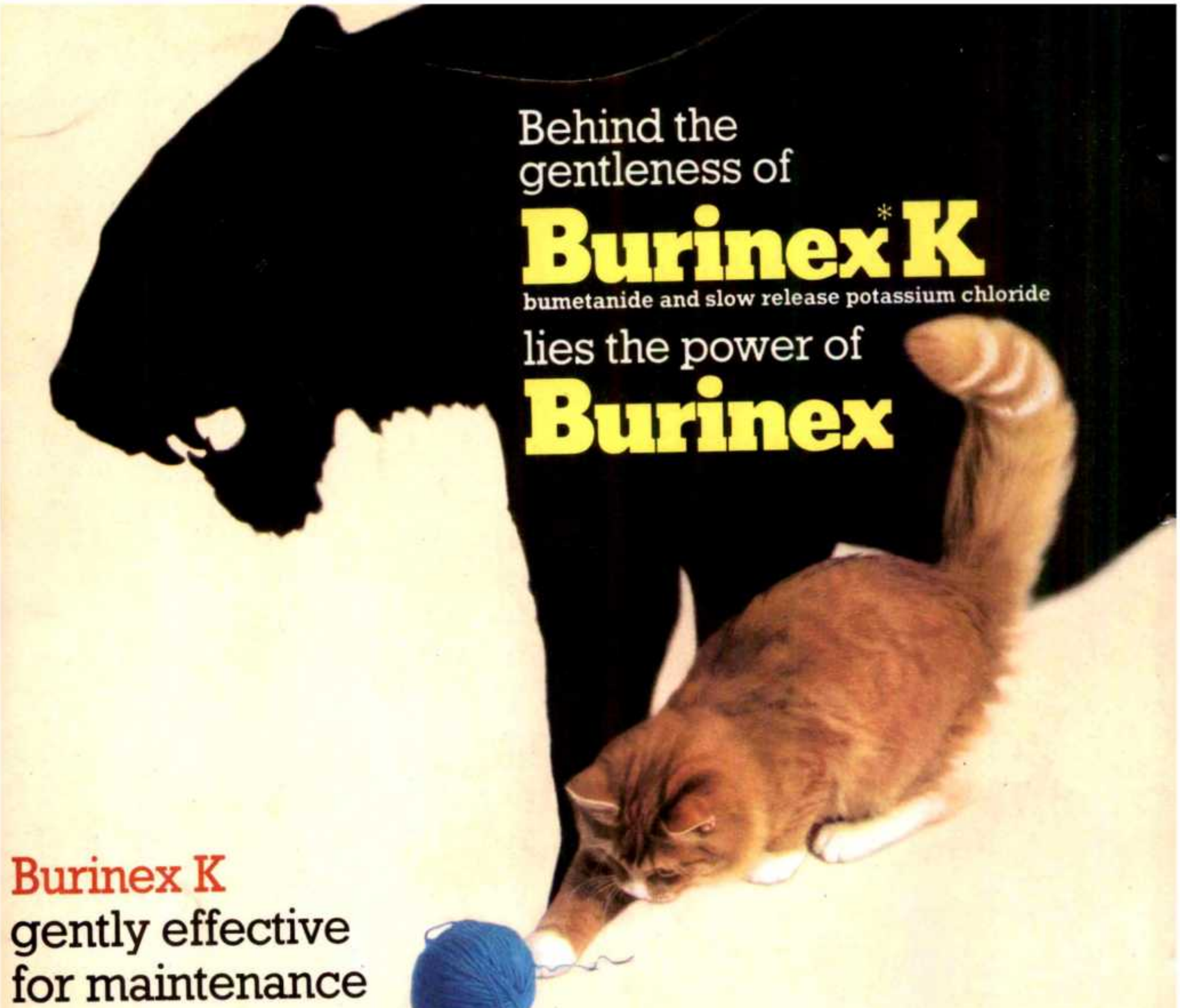

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History of atrial fibrillation 1628-1819. Harvey – de Senac – Laënnec *John McMichael* 193

Cardiac arrhythmias in hypertrophic cardiomyopathy *I Bjarnason, T Hardarson, S Jonsson* 198

Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs *R F Alvares, J F Goodwin* 204

"Torsade de pointes" tachycardia. Re-entry or focal activity? *C Naumann D'Alnoncourt, W Zierhut, B Lüderitz* 213

Significance of complete right bundle-branch block when an isolated finding. An echocardiographic study *M Dancy, G Leech, A Leatham* 217

M-mode echocardiographic features of endomyocardial fibrosis *B O George, F E Gaba, A I Tālabi* 222

Cross-sectional echocardiographic recognition of interruption of aortic arch between left carotid and subclavian arteries *J F Smallhorn, R H Anderson, F J Macartney* 229

Complete congenital heart block. Report of 35 cases. *J M Reid, E N Coleman, W Doig* 236

Absent left atrioventricular connection with right atrium connected to morphologically left ventricular chamber, rudimentary right ventricular chamber, and ventriculoarterial discordance. Problem of mitral versus tricuspid atresia *A Restivo, S Y Ho, R H Anderson, H Cameron, J L Wilkinson* 240

Total anomalous pulmonary venous connection. Repair using deep hypothermia and circulatory arrest in 44 consecutive infants *D F Dickinson, K M Parimelazhagan, M C K Tweedie, C R West, G P Piccoli, F Musumeci, D I Hamilton* 249

Routine radionuclide techniques in evaluation of patients with suspected coronary heart disease *E Thaulow, K Rootwelt, J Erikssen, S Nitter-Hauge* 255

Reversible ischaemia of right ventricle detected by exercise thallium-201 scintigraphy *A Lahiri, G P Carboni, J W Crawley, E B Raftery* 260

Coronary artery narrowing without irreversible myocardial damage or development of collaterals. Assessment of "critical" stenosis in a human model *Erling Falk* 265

Captopril as treatment for patients with pulmonary hypertension. Problem of variability in assessing chronic drug treatment *S Rich, J Martinez, W Lam, K M Rosen* 272

Left ventricular function in hypothyroidism. Responses to exercise and beta adrenoceptor blockade *J C Forfar, A L Muir, A D Toft* 278

A trial of prophylactic mexiletine in home coronary care *J A Bell, J M Thomas, J R Isaacson, N J C Snell, D W Holt* 285

Case reports

Rupture of a papillary muscle of the tricuspid valve. Echocardiographic diagnosis *R M Donaldson, M Ballester, A F Rickards* 291

Valve replacement for severe tricuspid regurgitation caused by Libman-Sacks endocarditis *J Laufer, M Frand, S Milo* 294

Congenital atresia of left coronary ostium *L G Van der Hauwaert, M Dumoulin, P Moerman* 298

Correspondence 301

Notices 308

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

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Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology 1977*. Edinburgh, London: Churchill Livingstone, 1978: 16-26.

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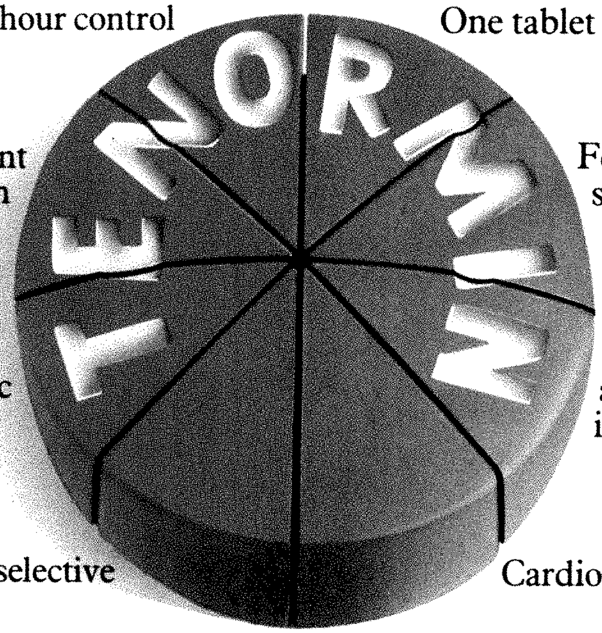

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NEW FROM BUTTERWORTHS

THE CONDUCTION SYSTEM OF THE HEART

M J Davies, MD, FRCPath
Professor of Cardiovascular Pathology, St George's Hospital Medical School, University of London
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Professor of Pathology, Department of Pathology, University of Amsterdam
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Clinical interest in the conduction system of the heart has grown apace since Professor Davies' first monograph in 1971.

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Neville Woolf, PhD, MB ChB, MMedpath, FRCPath
Bland-Sutton Professor of Histopathology, Middlesex Hospital Medical School, London and Honorary Consultant Pathologist, Middlesex Hospital, London

Atherosclerosis is a major cause of death in the developed world and is intensively studied by large numbers of clinical research workers. The volume of literature has grown at a great rate and is now so extensive that those not directly active in research find it difficult to appreciate the great advances made in our understanding of the atherosclerotic lesion.

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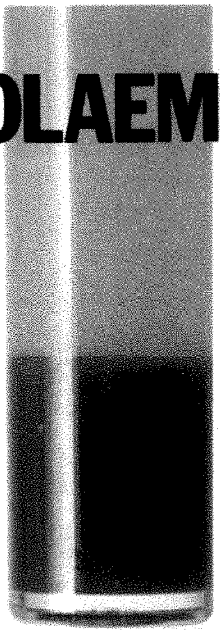

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History of atrial fibrillation 1628–1819
Harvey – de Senac – Laënnec

JOHN McMICHAEL

From The Wellcome Institute for the History of Medicine, London

SUMMARY For two centuries after Harvey the arterial pulse was often regarded as independent of the heart beat. This misunderstanding was mainly because of the frequent failure of the irregular heart to elicit a radial pulse: the "pulse deficit" of later times.

Harvey observed ineffective palpitation of the atrium just before death. This was probably atrial fibrillation. He established the origin of the heart beat in the right atrium.

Harvey's observations were confirmed and extended by de Senac in the mid-eighteenth century. He correlated gross irregularities (palpitation) with necropsy observation of mitral valve disease and dilatation of the left ventricle. He emphasised the origin of the heart's irregularity from the distended atrium consequent on distension or reflux of blood irritating the atrial wall.

He also commented on disconcerted action and rippling of the ventricular wall before final cessation of movement in a dying heart (ventricular fibrillation).

De Senac's ideas were a century and a half ahead of his time.

The problem of the pulse

In Chapter 3 of *De motu cordis* (Franklin's translation, 1957)[1] are laid out the logical reasons by which Harvey comes to the conclusion:

> there is just the one cause of arterial pulsation throughout the body, and that is contraction of the left ventricle. The pulsation of the artery-like vein (pulmonary artery) is similarly related to the contraction of the right ventricle . . . . In correspondence with the tension of the heart the arterial pulsations become larger, more forcible, frequent, rapid, while preserving the rhythm, volume and order of the heartbeat . . . . For the pulse of the arteries is nothing save the impulse of the blood entering these vessels.

This clear understanding had to wait nearly 200 years for further application in the precise study of cardiology. It was debated, and often misunderstood by practitioners of medicine, and indeed Abercromby (1685) in a book on the pulse,[2] said: "Its source is as mysterious as the source of the Nile".

The belief, held by many, that arteries had an inherent movement of their own was even supported by Laënnec (1819). In discussing "intermission of the pulsation of the heart", he noted variations in the heart's contractions with or without a palpable pulse and commented as follows:

> Many considerations prove that the mere examination of the pulse is insufficient to inform us of the state of the circulation and must often lead us into error . . . .
>
> After what has been said and after its general uncertainty avowed by the most experienced practitioners it may seem surprising that the practice of feeling the pulse has been so generally followed in all ages. The reason for this practice is, however, sufficiently obvious. It is easy of performance and gives little inconvenience either to the physician or to the patient . . . . The facts above stated relative to the discordance existing between the pulsation of the heart and of the arteries, more especially as to strength, are contrary to the more general opinion of modern physiologists who consider the action of the arteries as entirely dependent on that of the heart. Bichât himself has fallen into this error.
>
> (Laënnec, Forbes' translation, 1821).[3]

Marie François Bichât (1771–1802) was the distinguished anatomist to the Hôtel Dieu, whose observations were much quoted by Laënnec. Bichât promoted the study of tissues and membranes before the era of the microscope. Thus the "pulse deficit" of atrial fibrillation seems to have contributed to the centuries long failure of the profession to accept Harvey's firm demonstration that the beating heart created the pulse. Sometimes the beat was too weak to be felt at the radial artery.

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Origin of the heart beat

Harvey's meticulous observations (chapter 4, Franklin's translation[1]) had already established that the heart beat was initiated in the atria, and the right atrium in particular. From his many direct observations on the heart in animals, fishes, frogs, eels, birds, and domestic animals, Harvey gives the following account:

> The movement is seen to begin from the auricles and to pass on to the ventricles. With everything becoming more sluggish as the heart lies dying, and also in fishes and the colder blooded animals, these two movements become separated by an interval of inactivity . . . . Finally as it sinks to death (the ventricle) ceases to reply with a proper movement to the pulsating auricle. The heart (i.e. ventricle) ceases to beat before the auricles so that the auricles may be said to outlive it . . . . With all the other parts inactive and dead the right auricle goes on beating so that life appears to linger longest in this auricle . . . . If at this time you cut the apex of the heart with a pair of scissors you will see blood flow out from the wound with each beat of the auricle. You will thus realize that the blood gets into the ventricle not through any pull exerted by the distended heart but through the driving force exerted by the beat of the auricles.

Harvey continued:

> But I . . . have noticed, that after the heart proper, and even the right auricle were ceasing to beat and appeared on the point of death, an obscure movement, undulation/palpitation had clearly continued in the right auricular blood itself for as long as the blood was perceptibly imbued with warmth and spirit.

Harvey must thus be credited with the first direct observation of a fibrillating atrium.

Richard Lower (1631–1691) began as research assistant to Thomas Willis and was introduced into the Royal Society by Boyle. He was the best English physiologist after Harvey and later practised medicine in London. He showed that blood changed colour to bright red in passage through the lungs and that asphyxia prevented this. He laid down in his *Tractatus de Corde* (1669, p. 75),[4] "The heart is definitely a muscle and has movement exactly similar to other muscles. It receives spirits from the abundance of nerves which are inserted into it".

Vital spirits from the nervous system were supposed to animate the nerves. The idea of nervous origin of the heart beat was to persist for another two centuries.

De Senac's critical analysis

In the mid eighteenth century a new dimension of analysis was added by de Senac (Fig) whose views were much in advance of his time. He built his physiological ideas on the basis of Harvey and Lower, repeating their experiments and applying critical analytical thought.

Jean-Baptiste de Senac (1693–1770), MD Montpellier, became physician to Louis XV and also became a Councillor of State. In 1749 his *Traité de la Structure du Coeur de son action et de ses maladies* (S) was published and a second edition appeared in 1774.[5] This is the first textbook on cardiology. Volume I contains the most detailed account of the anatomy of the heart in adult and in fetal life and the problems of its physiology are considered thoroughly in Volume II. He also published a more concise *Traité des Maladies du Coeur* (M) in two editions (1774–1783). It is from the second edition and second volume of S and M ("structure" and "maladies") that the following extracts are made. The posthumous editions were guided through the press by Baron Antoine Portal, but the text had been revised by the author.

De Senac confirmed Harvey (S, p. 149) that in the heart of a dog dying after severing an artery, beating persists longest in the right atrium and also in the termination of the vena cava. Thus the *ultimum moriens* part of the heart was confirmed in the sino-atrial region.

Although de Senac built on the ideas of Richard Lower that the heart was innervated like other muscles, he asked many difficult questions: why can the heart contract after death? (S, p. 102). Cut the nerves and the heart does not stop? de Senac established irritability of the heart. Touching the heart may make it contract even more strongly. It will contract in response to internal pressure: compare the intestines. He was mystified by the visible contraction of the non-innervated embryo heart of the chick, which he thought might be the result of some still unknown agency. The debate about nervous control of the heart beat continued for another century and a half.

Just as Harvey had seen fibrillation of the atria in a dying heart, de Senac gave a description of terminal fibrillation of the ventricles (S, p. 151):

> Before these parts (of the heart) lose their action the harmony of their movements is disconcerted: there is neither order nor regular succession . . . . When their (muscle) mass no longer makes any effort their fibres are still agitated. They form oblique ripples and there is seen, according to Pechlin, an undulation of many varieties moving from the base to the apex in a spiral form following no doubt the direction of the superficial fibres.

Johannis Nicolai Pechlin (1646–1706) observed death in an open chest wound (*Historia Vulneris Thoracici*, 1683[6]). Born in Holland, he practised in Kiel.

JOANNES SENAC ARCHIATRORUM COMES.

Fig *Jean Baptiste de Senac (1693–1770), Courtesy of the Wellcome Trustees.*

Clinico-pathological correlations

When he turned his attention to clinical abnormalities of the heart, de Senac was linking his observations with pathological anatomy in the same way as Morgagni, his slightly older contemporary.

Giovanni Battista Morgagni (1682–1771), was Professor of Theoretical Medicine at Padua from 1720 until his death. He published his book on *The Seats and Causes of Diseases investigated by Anatomy* in 1761. This established a pattern of observation by which the clinical manifestations of disease might be better understood.

De Senac devoted much attention to palpitation and his necropsy correlations are best described in his *Traité des Maladies du Coeur.*[7] He emphasised mitral valve disease in the causation of palpitation. His morbid anatomical observations are precise. Under 'The particular and proximate causes of palpitation are in the heart or in the vessels':

> Cardiac causes are disorders of its very substance or of the valves. In one word obstacles which retain the blood in the ventricles and which under continuous pressure irritate the heart fibres causing stronger contractions. Reflux of blood into the auricles causes contractions of greater force, necessarily precipitating palpitations. When the obstacles in the heart obstruct the entrance to the ventricles, blood accumulates in the cavities of the auricles and irritates the fibres of their walls. Their contractions become more lively. (M, p. 7–9).

De Senac quotes a case with irregularity of the heart where the tricuspid valve was "narrowed" in the same manner as that described by Vieussens in the mitral valve (M, p. 9). He gives another description of necropsy in which "the tricuspid valve was narrowed and cartilaginous" and "the mitral valve was narrowed, stuck down to the inner surface of the ventricle and adherent to its walls. The chordae tendineae were shortened, rendering the cusps immobile" (M, p. 10). This is a precise description of a "funnel" stenosis and regurgitation of the mitral valve. Then he goes on:

> Dilatation of the ventricles may also cause palpitations. This results from obstruction of the exit of blood which distends the ventricles which thus contract strongly causing more violent reflux into the auricles. (M, p. 11).

These repeated references to distension of the atria and the precipitation of contractions by pressure of the accumulating blood were somewhat prophetic of the ideas developing in the early nineteenth century when the irregular pulse of atrial fibrillation was usually regarded as a diagnostic sign of mitral stenosis, which was indeed its commonest cause. De Senac's observations had, however, also related the irregularity to enlargement of the ventricles as well. But even here he comes back to the effect of ventricular dilatation on reflux of blood into the atria.

In his discussion of palpitation in general, de Senac's remarks are full of observational clinical wisdom:

> Palpitations consist of beats which are either more active and more frequent, such as occur in fever or in any action demanding effort, and even mental agitation. But these are not illnesses by themselves and do not leave any sequential damage. When the body settles down to rest the heart resumes its normal beat. (M, p. 2).

He concluded that the nerves of the heart were important in the precipitation of palpitation:

> There are, however, palpitations which are lively, and irregular beats agitate the heart. The complaint is produced by various fortuitous events and often appearing without any obvious cause, settling down with rest, but possibly recurring. We only define as palpitations beats which are lively, irregular, agitate the heart and form a veritable malady of the beat of the heart . . . continuing during rest . . . . (M, p. 2).
>
> When the palpitations are irregular they form a veritable malady of the beat of the heart acting on the great arteries. The primary cause of the disorder is an irritation . . . of the tissues of the heart and a reflux of blood which is directed against the auricles with more violence . . . . The irritation is followed by contraction of the muscle and the greater the force of the ventricles the more the reflux . . . . (M, p. 5).
>
> The reflux agitates the heart or disturbs its action. (M, p. 6).
>
> If the auricles are strained and increased in volume they cause palpitations . . . . On exercise too much blood arrives at the sinus of the vena cava . . . its walls are irritated by the overload of blood which is driven more forcibly to the right ventricle and its action becomes more lively: hence a reflux which is still more violent and beats in response to this reflux. One sees the same effects when the auricles are abnormally dilated . . . their walls are more irritable and they act more actively on the ventricles. (M, p. 12–13).

In the case of the funnel valve described above,

> The ventricles send a violent reflux into the auricles. Distension of the walls of the heart makes palpitations inevitable. (M, p. 11).

In dealing with palpitation he points out that irregularities can be precipitated by distension of the stomach, which could be relieved by the use of various carminatives, and he noticed that the remedy whose effects have appeared to be the most constant and the most prompt in many cases is quinine mixed with a little rhubarb. "Long and rebellious palpitations have ceded to this febrifuge, seconded with a light purgative". This is quoted by Willius and Keys[8] from his first edition of 1749, and is prophetic of the current rational use of quinidine first observed and noted by an astute physician. De Senac's other deep insights have had little mention in medical historical texts.

De Senac's remarkable insights into the correlations of mitral disease with gross pulse irregularities were based on his own observations on cardiac muscle irritability and the atrial origin of the heart beat as established by William Harvey and expanded by de Senac's own meticulous observations. He stood firm on the atrial origin of the heart beat as established by William Harvey. Like Harvey he also put much emphasis on the development of rippling movements in the dying chambers of the heart atria and also ventricles. These are probably the earliest experimental observations of fibrillation. He commented, however

(S, p. 52), that "the causes of palpitation are not the causes of the natural heart-beat", thereby hinting at their ectopic origin.

De Senac advanced understanding to its very limits in his day in exemplary observation and deep critical thought. He also commented on the speculative writings of others: "Rien n'est plus rare que l'exactitude d'observation" (M, p. 8).

Note: The author is responsible for the selection of quotations and translation.

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Cardiac arrhythmias in hypertrophic cardiomyopathy

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SUMMARY This study was designed to assess the prevalence of cardiac arrhythmias in a group of relatives of patients who had come to necropsy with hypertrophic cardiomyopathy. Another aim of the study was to assess the validity of an interventricular septal thickness of 1·3 cm or more, measured by echocardiography, as a diagnostic criterion of hypertrophic cardiomyopathy among relatives of cases proven at necropsy. Fifty close relatives of eight deceased patients were examined. By the above definition 22 relatives had hypertrophic cardiomyopathy and 28 did not. A comparison of the prevalence and types of cardiac arrhythmias, as shown by 24 hour ambulatory electrocardiographic monitoring, was made between the two groups and a third apparently healthy group of 40 people. The patients with hypertrophic cardiomyopathy showed a significant increase in supraventricular extrasystoles/24 hours, supraventricular arrhythmias, high grade ventricular arrhythmia, and the number of patients with more than 10 ventricular extrasystoles every 24 hours when compared with the other groups. There was no significant difference between normal relatives and controls. The prevalence and types of arrhythmia in these patients were similar to those found by other investigators using different diagnostic criteria. These results support the contention that these patients do indeed have hypertrophic cardiomyopathy and suggest that all close relatives of necropsy proven cases should be examined by echocardiography and subsequently by ambulatory electrocardiographic monitoring if the interventricular septal thickness is 1·3 or more.

Patients with hypertrophic cardiomyopathy frequently die suddenly and unexpectedly, presumably from cardiac arrhythmias.[1-3] In a recent Icelandic study the inheritance pattern of hypertrophic cardiomyopathy was described.[4] The diagnosis was based on inordinate interventricular septal thickening ($\geq$1·3 cm). Most of the patients had no symptoms, and were only identified after necropsy findings suggesting hypertrophic cardiomyopathy in a close relative. No single echocardiographic marker, however, is pathognomic for hypertrophic cardiomyopathy.[5-7] It has been suggested that an interventricular septal thickness cut-off point at 1·3 cm may be both too sensitive and non-specific as a diagnostic criterion.[8-10]

To study the validity of this echocardiographic criterion we have compared the prevalence and types of cardiac arrhythmias in the group of relatives who had an interventricular septal thickness of 1·3 cm or more in relation to those relatives whose septum was thinner than 1·3 cm.

Patients and methods

Our previous study included 58 close relatives of eight patients (out of a total of 11) who had necropsy criteria of hypertrophic cardiomyopathy in Iceland during the years 1966 to 1977.[4] The eight index patients were male patients and all died suddenly from cardiac causes except one who died in an accident.[11] Their average age at the time of death was 29 years (3 months to 47 years) and only two had had symptoms previously.

Twenty-three relatives had echocardiographic criteria ($\geq$1·3 cm) of hypertrophic cardiomyopathy. Of these, 22 were investigated by 24 hour electrocardiographic monitoring: 16 men (12 first degree and four second degree relatives of deceased patients) and six women (five first degree and one second degree). Their average age was 50 years (18 to 83 years). Table 1 shows their sex, age, symptomatic status, electrocardiogram, and echocardiographic findings and cardiac arrhythmias. Nineteen were in New York Heart Association[12] class I, two were in class III, and one in class IV. A male patient in class III complained of dyspnoea and dizziness on mild exercise. A woman, previously thought to have ischaemic heart disease, complained of angina pectoris and shortness of breath. She had a typical systolic anterior motion of the mitral valve as well as interventricular septal thickening. A woman in class IV had a long history of

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Table 1 *Summary of clinical, electrocardiographic, echocardiographic, and 24 hour ambulatory electrocardiographic findings in 22 patients with hypertrophic cardiomyopathy*

Case No.	*Sex*	*Age (y)*	*Symptomatic status*[12]	*Electrocardiographic findings*†	*Echocardiographic findings (cm)*			*Rhythm disturbances*		*No. of ventricular extrasystoles*
					IVS	*LVPW*	*IVS/LVPW*	*Atrial*	*Ventricular*	
1	M	83	I	AF	2·4	1·4	1·7	AF	I	4
2	M	82	I	I° AVB	1·5	0·8	1·8	PAF	III	93
3	M	71	I	LVH	1·4	1·2	1·2	PAF	IV B	8608
4	M*	70	I	LVH	1·4	1·5	1·0		IV B	116
5	F	67	III	LVH,Q I° AVB	2·25	1·1	2·0	SVT	IV A	42
6	F	64	IV	LVH	1·5	1·2	1·25	SVT	III	312
7	F	63	I	LVH,Q	1·75	1·0	1·75	SVT	III	641
8	F	61	I		1·5	1·0	1·5		III	23
9	M	60	I		1·4	1·3	1·1		I	2
10	M	58	III	LVH	1·3	1·0	1·3		I	7
11	M*	55	I	LVH	2·0	1·2	1·7	SVT	I	87
12	M	53	I	ICD	1·8	1·1	1·7		IV B	483
13	F*	51	I	I° AVB	1·4	1·0	1·4		III	9
14	F	47	I	LVH,Q	1·6	1·0	1·6		III	122
15	M	45	I	Left atrial abnormality	1·6	0·8	2·0	I	9	
16	M	31	I	LVH	1·4	1·0	1·4	SVT	0	0
17	M	26	I		1·5	1·2	1·25		III	15
18	M*	25	I	LVH	1·3	1·0	1·3		I	1
19	M	24	I	LVH	1·5	1·4	1·1		III	20
20	M	23	I	LVH	1·5	0·9	1·7		0	0
21	M*	20	I	LVH	1·5	1·3	1·2		IV A	8
22	M	18	I	LVH	1·4	0·9	1·6		III	7

*Second degree relatives of patients who died with hypertrophic cardiomyopathy and came to necropsy, otherwise first degree relatives.
†Classifications of Ryan *et al.*[16]
AF, atrial fibrillation: I° AVB, first degree atrioventricular block; ICD, intraventricular conduction defect; IVS, interventricular septum; LVH, left ventricular hypertrophy; LVPW, left ventricular posterior wall; PAF, paroxysmal atrial fibrillation; Q, abnormal Q waves; SVT, supraventricular tachycardia.

tiredness. She had a cardiac catheterisation in 1980 showing normal coronary arteries.

A 12 lead electrocardiogram showed left ventricular hypertrophy in 14 (64%) patients, using Romhilt-Estes[13] and/or Sokoloff's criteria.[14] Three had abnormal Q waves,[14] three had a long PR interval (>0·20 s), one had an interventricular conduction delay,[14] and one had an enlarged left atrium.[15] Only one patient had a rhythm disturbance on a conventional electrocardiogram (atrial fibrillation). Another patient in sinus rhythm had had atrial fibrillation earlier. He was being treated with quinidine.

Twenty eight close relatives of deceased patients with hypertrophic cardiomyopathy had normal echocardiographic findings (interventricular septal thickness <1·3 cm): nine men (four of them second degree) and 19 women (two second degree). Their average age was 39 years (10 to 82 years). None of these had any signs or symptoms of heart or lung disease, and their electrocardiograms were normal.

A further control group was composed of 20 men and 20 women, all hospital employees. None of them had symptoms suggesting cardiac or pulmonary disease. In all, physical examination was normal and their electrocardiograms and echocardiographic examinations did not disclose any abnormalities. Their interventricular thicknesses were 1·2 cm or less.

In all three groups, ambulatory 24 hour electrocardiographic recordings were performed, using one-channel Oxford Medilog recorders. All subjects were instructed to record their activities and complaints at least hourly during waking hours. A Reynolds High Speed Pathfinder machine was used for arrhythmia analysis. The same physician (IB) analysed and classified all the recordings.

Ventricular arrhythmias were classified according to Ryan *et al.*[16] (Table 2). Unless otherwise stated, Fisher's exact test for 2×2 tables was used to assess statistical significance.

Results

Fig. 1 shows the total number of supraventricular extrasystoles during 24 hours in patients with hypertrophic cardiomyopathy, in their relatives, and in the control group. Seven patients with hypertrophic car-

Table 2 *Grading of ventricular extrasystoles (VE) of Ryan et al.*[16]

Class	*Character of ventricular arrhythmia*
0	No VE/24 h
I	Occasional <30/h
II	Frequent >30/h
III	Multiform
IV A	Couplets (two consecutive VE)
IV	Ventricular tachycardia (three or more consecutive VE)

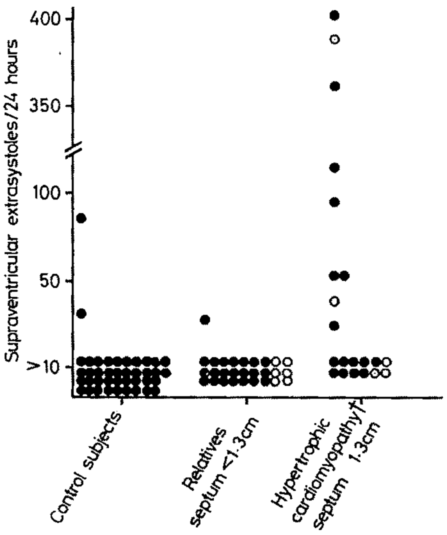

Fig. 1 *Number of supraventricular premature beats during 24 hour ambulatory electrocardiographic monitoring in an apparently healthy control group, in relatives without hypertrophic cardiomyopathy, and in 21 patients with hypertrophic cardiomyopathy.*
†One patient with atrial fibrillation excluded.
Open circles indicate second degree relatives of patients who died with hypertrophic cardiomyopathy and came to necropsy, closed circles first degree relatives.

diomyopathy had 50 or more extrasystoles, but only one in the control group and none in the group of relatives. The number of patients with cardiomyopathy who had more than 50 supraventricular extrasystoles was significantly greater than in the other two groups ($p<0\cdot02$).

Two control subjects and one relative had episodes of supraventricular arrhythmia as compared with eight in the group with hyprtrophic cardiomyopathy ($p<0\cdot003$). Two had paroxysms of atrial fibrillation and five had supraventricular tachycardia, each episode lasting less than 10 seconds. One patient had constant atrial fibrillation. He had several RR intervals lasting up to three seconds (Fig. 2). Six out of eight patients with supraventricular arrhythmias were over 60 years of age, compared with two out of 14 under 60 years of age ($p<0\cdot01$).

Fig. 3 shows the classification of ventricular arrhythmias. Fourteen (64%) of the patients with hypertrophic cardiomyopathy were in classes III and IV. Three of them had episodes of ventricular tachycardia (Fig. 4), in each case lasting less than three seconds (nine beats). Six patients were in class 1 and only two had no ventricular arrhythmias. In the control group, one subject was in class III and one in class IVA. Sixteen were in class I, however, and 22 (55%) had no ventricular arrhythmia. In the group of relatives two subjects were in class II, nine in class I, and 17 (61%) had no ventricular arrhythmias. The occurrence of high grade arrythmia (III or higher) was significantly more common ($p<0\cdot0001$) in the group

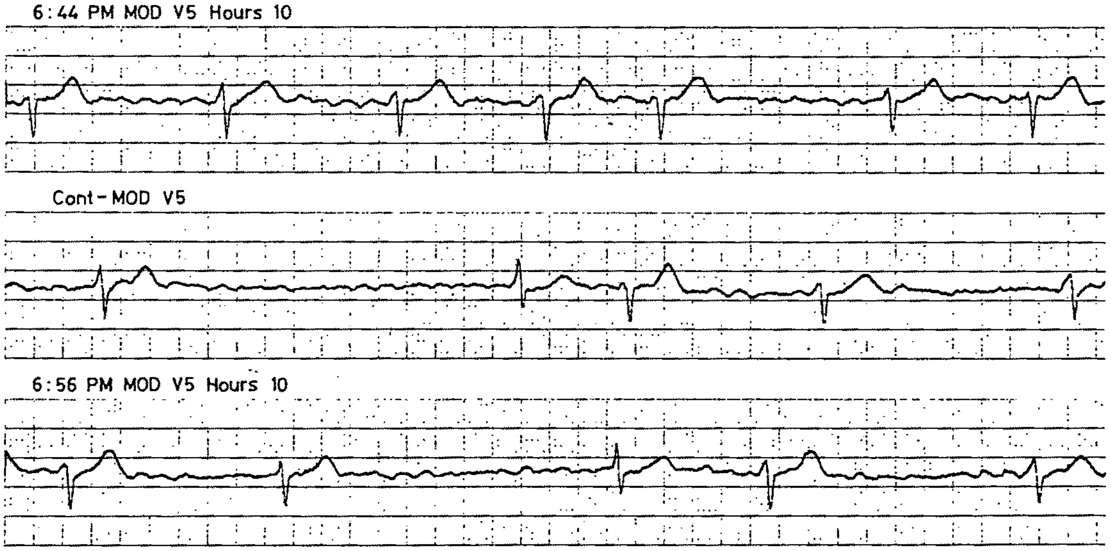

Fig. 2 *A strip from an ambulatory electrocardiographic recording of a patient with established atrial fibrillation showing a period of asystole of three seconds duration.*

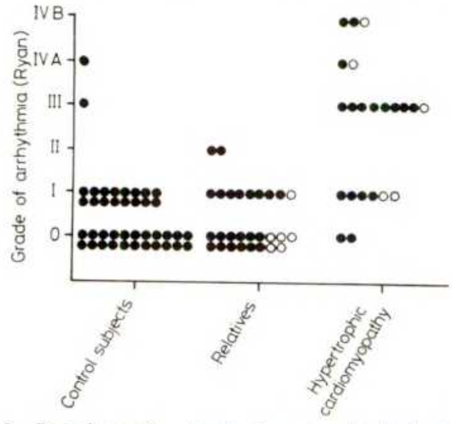

Fig. 3 *Prevalence of ventricular premature depolarisation grade during 24 hour ambulatory electrocardiographic recording in an apparently healthy control group, in relatives without hypertrophic cardiomyopathy, and in 22 patients with hypertrophic cardiomyopathy.*
Symbols as in Fig. 1.

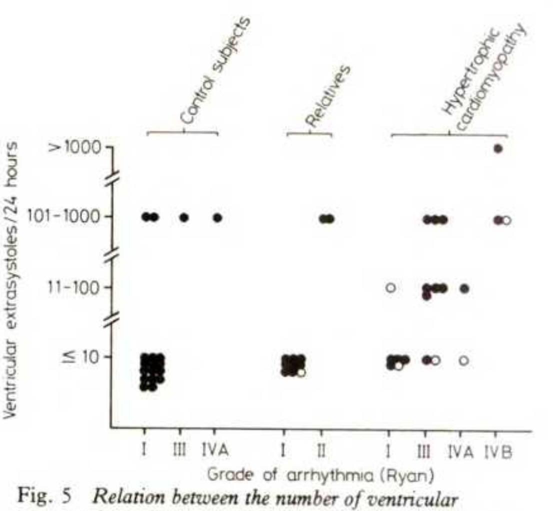

Fig. 5 *Relation between the number of ventricular extrasystoles in 24 hours and the grade of arrhythmia in the control group, in relatives without hypertrophic cardiomyopathy, and in patients with hypertrophic cardiomyopathy.*
Symbols as in Fig. 1.

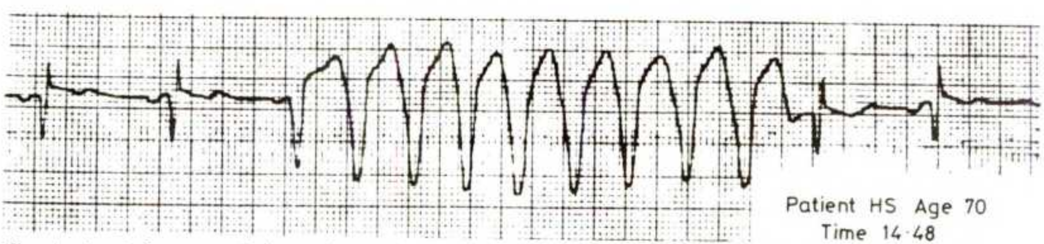

Fig. 4 *A strip from an ambulatory electrocardiographic recording from an asymptomatic patient. A short burst of ventricular tachycardia (3 s) is shown.*

with hypertrophic cardiomyopathy compared with normal relatives or control subjects. There was no significant difference between normal relatives and control subjects.

Multiple regression techniques did not show a statistically significant relation between the grade of arrhythmia and age or interventricular septal thickness.

Fig. 5 shows the relation between the ventricular arrhythmia classification and the total number of ventricular extrasystoles during 24 hours. Twelve (55%) patients with hypertrophic cardiomyopathy had more than 10 ventricular extrasystoles in 24 hours but only four (10%) out of the control group and two (7%) in the group of relatives. The cardiomyopathy group differed significantly from the others in this respect ($p<0{\cdot}001$) while there was no difference between normal relatives and control subjects. The number of subjects with 100 or more ventricular extrasystoles every 24 hours, however, did not differ significantly between the groups. All the most serious ventricular arrhythmias occurred during waking hours. Four patients complained of dizziness and palpitation during the recording. The timing of such complaints, however, did not coincide with the occurrence of serious arrhythmias.

Discussion

This study showed a high incidence of cardiac arrhythmias among symptom-free patients or those with mild symptoms with a thick ventricular septum and close familial links with deceased patients with hypertrophic cardiomyopathy compared with their normal relatives and a normal group. The arrhythmias were always unexpected and not felt by the patients, even in three people with ventricular tachycardia. The common occurrence of arrhythmias in this group supports our previous contention that most of them do indeed suffer from cardiomyopathy.[4]

Table 3 *Previous 24 to 48 hour ambulatory electrocardiographic studies on patients with hypertrophic cardiomyopathy compared with our study*

Author	*No. of cases*	*AE*	*Supraventricular* arrhythmia*	*VE*	*Ryan*[16] ≥III	*VT*
McKenna *et al.*[17]	30	84%	41%	90%	50%	17%
Canedo *et al.*[18]	33	70%	36%	82%	47%	15%
Savage *et al.*[19]	100	54%	15%	83%	65%	19%
Present series	22	68%	32%	91%	64%	14%

*Patients with established atrial fibrillation excluded.
AE, atrial extrasystoles; VE, ventricular extrasystoles; VT ventricular tachycardia.

Table 3 shows our results in comparison with those of other authors. McKenna *et al.*[17] studied 30 consecutive patients. The patients of Canedo *et al.*[18] had significant symptoms. One third of the patients reported by Savage *et al.*[19] had no symptoms and two thirds had symptoms consistent with hypertrophic cardiomyopathy. They found little difference in arrhythmias between the two groups and, on the whole, the four studies show an interesting conformity, though the selection of patients varied. Our results support those of Savage *et al.*[19] who found that the correlation between symptoms and cardiac arrhythmias in hypertrophic cardiomyopathy is poor.

The annual attrition rate in hypertrophic cardiomyopathy is 3 to 4%.[2,20] Maron *et al.*,[3] in their study of 26 patients who had died suddenly and unexpectedly, could not identify any physical signs or haemodynamic variables of prognostic importance. All of their patients, however, had an abnormal electrocardiogram, and an unusually thick interventricular septum (mean 25 mm, range 17 to 55 mm). One third of their patients had a family history of sudden death. Another study[21] illustrated, similarly, that electrocardiographic and haemodynamic findings offered no predictive value, but youth combined with a family history of hypertrophic cardiomyopathy and/or sudden death was a poor prognostic feature. Despite different patient selection and the moderate increase in interventricular septal thickness (mean 17 mm) of our patients it is possible that they form an unfavourable prognostic group because of their family history.

Our study does not show the extent to which cardiac arrhythmias discovered by 24 hour electrocardiographic monitoring may influence the future course of patients with hypertrophic cardiomyopathy. McKenna *et al.*[22] have recently reported ventricular tachycardia with multiform and paired ventricular extrasystoles in five patients who died subsequently. In addition, a follow-up study on the patients of Savage *et al.*[19] showed that there was a significant increase in sudden deaths among patients with asymptomatic ventricular tachycardia.[23] The microscopical disorganisation of muscle cells in hypertrophic cardiomyopathy[24] may conceivably offer a fertile medium for the initiation and maintenance of re-entry mechanisms leading to ventricular tachycardia or fibrillation. It is also possible that pre-excitation may be of importance in this context, as suggested by Krikler *et al.*[25] and Bouhour *et al.*[26] It therefore seems justifiable to hope that vigorous antiarrhythmic treatment under these circumstances may prevent sudden death in some cases. Recent trials using amiodarone appear particularly promising.[27] The results of this study also suggest that relatives of patients with hypertrophic cardiomyopathy should be investigated with echocardiograms and then ambulatory 24 hour electrocardiographic recording, if there is a thickened interventricular septum. Finally, our study shows that many patients with hypertrophic cardiomyopathy will remain undiagnosed unless effective objective screening methods are applied to individuals judged to be particularly at risk.

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Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs

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SUMMARY Beta adrenergic blocking drugs in hypertrophic cardiomyopathy provide symptomatic relief but their effect on long-term prognosis is uncertain.

Thirty patients were studied non-invasively by simultaneous recordings of echocardiogram, apexcardiogram, phonocardiogram, and electrocardiogram in order to assess diastolic abnormalities on and off oral beta adrenergic blocking drugs. While on treatment these patients had a mean dose of propranolol 200 mg/day. The treatment was stopped for one week and then non-invasive assessment was repeated.

The following diastolic time intervals were studied: isovolumic relaxation period (A_2–mitral valve opening); rapid relaxation period (A_2–O point of the apexcardiogram), and the period from mitral valve opening to the O point of the apexcardiogram (Mo–O) when most of the filling of the left ventricle occurs. The prolongation of the rapid relaxation period reflects a reduced rate of fall of the left ventricular pressure when the pressure differential does not change between A_2 and the O point of the apexcardiogram, and in this study this period was prolonged in 19, shortened in eight, and remained the same in three patients after beta blockade. The Mo–O point was prolonged in 22, shortened in seven, and was unchanged in one patient after beta adrenergic blocking drugs. All these results were independent of heart rate.

In conclusion the response of diastolic time intervals to beta blocking drugs in hypertrophic cardiomyopathy was variable but there was a significant number of patients in whom the time available for filling of the left ventricle was prolonged, suggesting better filling possibly because of improved distensibility of the left ventricle after beta adrenergic blocking drugs.

For the past two decades beta adrenergic blocking drugs have been widely used in the treatment of hypertrophic cardiomyopathy and since early trials they have been shown to produce important symptomatic benefits.[1–3] A double blind trial of practolol, propranolol, and a placebo has suggested that beta blockade was associated with amelioration or disappearance of dyspnoea, anginal pain, and syncope in severely symptomatic patients[4] but unfortunately beta adrenergic blockade cannot be guaranteed to prevent sudden death.[5 6]

Hypertrophic cardiomyopathy is a disease characterised by massive hypertrophy and impaired distensibility of the left ventricle which leads to abnormal diastolic filling with a small systolic cavity and a very stiff ventricle.[7–9]

We believe that this abnormal diastolic filling is the most important factor in determining symptoms and prognosis regardless of whether a gradient between the outflow tract of the left ventricle and aorta is present or not.

It has been known that beta adrenergic stimulation increases the pressure gradient between left ventricle and aorta and decreases the calculated orifice size of the outflow tract of the left ventricle. Such stimulation may be produced or be augmented by exercise, tachycardia, emotion, and drugs that have a positive inotropic effect.[10 11]

Therefore it was thought initially that this improvement of symptomatology was the result of a decreased pressure gradient across the outflow tract

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with a lower cardiac output, in proportion to the decrease in heart rate,[12] but subsequent workers have shown by invasive[13 14] and non-invasive[4 6 15] methods that the important mechanism of action of beta blockade was an increase in left ventricular distensibility, allowing the inflow of an increased volume of blood during diastole.

One of the difficulties in interpreting the value of these drugs has been the lack of objective assessment of the results of oral treatment.

Therefore in the present study an attempt was made to study filling and relaxation, the two main interdependent events in early diastole, in hypertrophic cardiomyopathy on and off oral beta adrenergic blocking drugs, in order to detect any important changes after beta blockade.

We have studied the events during diastole using simultaneous non-invasive recordings of the left ventricle and mitral valve echocardiogram, apexcardiogram, phonocardiogram, and electrocardiogram.[16]

Subjects and methods

Observations were made on 30 patients who fulfilled the clinical,[7] electrocardiographic,[17] echocardiographic,[18 19] and angiographic criteria for hypertrophic cardiomyopathy. All these patients were in attendance at Hammersmith Hospital and their clinical details are given in Table 1. The group included eight women and 22 men with a mean age of 44 years (range from 14 to 63 years). Twenty-four patients were in sinus rhythm and six in atrial fibrillation. Twelve patients had a left venticular outflow tract gradient at rest, seven had a gradient only on provocation, and 11 patients had no demonstrable gradient. None of these 30 patients was in cardiac failure.

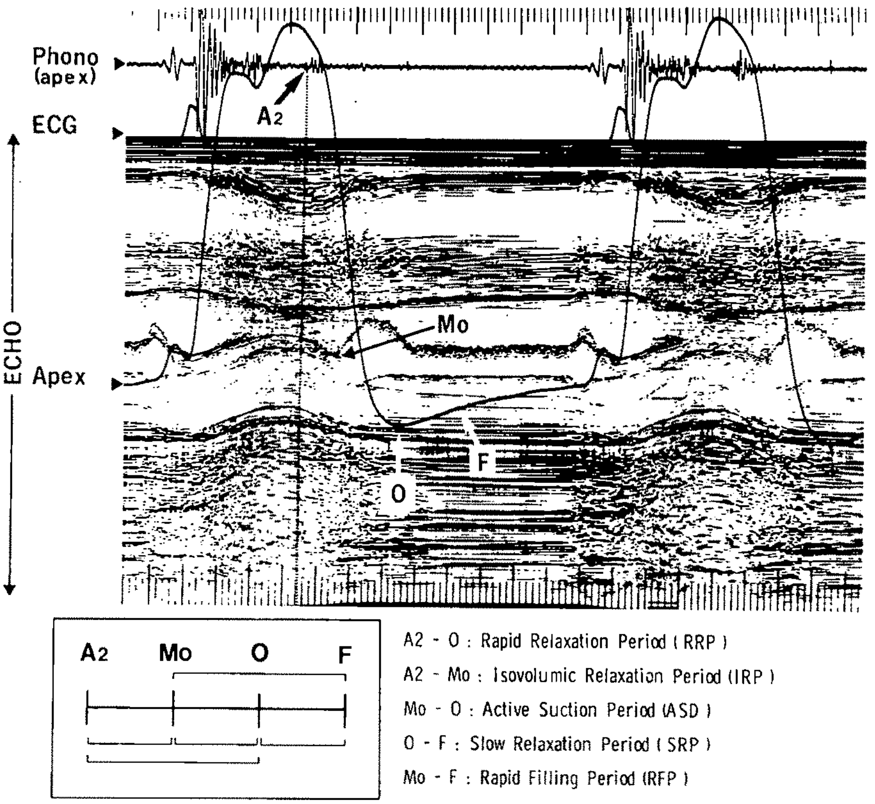
Of these 30 patients, propranolol (mean dose of 230 mg/day) was being taken by 20 patients; oxprenolol and metoprolol were being taken by five patients each in a mean dosage of 252 mg and 130 mg/day, respectively. The latter drugs were used because of intolerance to propranolol. All these patients were on beta adrenergic blocking drugs for at least one month (when initially studied with non-invasive techniques). The treatment was then stopped for one week and the non-invasive assessment was repeated.

These 30 patients were studied with simultaneous recordings of apexcardiogram, left ventricular and mitral valve echocardiogram, phonocardiogram, and electrocardiogram (Fig. 1).

The subjects lay comfortably in the left lateral recumbent position in the moveable angiography cradle with their head and shoulders raised (15–20°). The left arm was raised so that the apex beat could be easily located. The right arm rested along the right side and the cradle was rotated between 30 and 60° to the left in order to ensure the best quality of the apexcardiograms and echocardiograms. Measurements

Table 1 *Clinical details of 30 patients studied on and off beta blocking drugs*

Case No.	*Age*	*Sex*	*Rhythm*	*Heart rate (beats/min)*	*Gradient at rest*	*Gradient on provocation*	*Drug*	*Dosage (mg/day)*
1	60	M	SR	56	+	+	Propranolol	120
2	36	M	SR	81	+	+	,,	800
3	42	M	SR	74	–	–	,,	80
4	32	M	SR	58	–	+	,,	240
5	48	M	SR	61	–	–	Metoprolol	100
6	32	F	SR	53	–	–	Propranolol	30
7	41	M	SR	72	–	–	,,	120
8	37	M	SR	63	+	+	Oxprenolol	240
9	38	F	SR	69	+	+	Propranolol	60
10	46	F	SR	48	–	+	,,	120
11	55	M	SR	56	+	+	Oxprenolol	240
12	46	M	SR	65	–	+	Metoprolol	200
13	44	M	SR	66	–	–	Propranolol	80
14	43	M	SR	66	–	–	,,	240
15	51	M	AF	86	–	–	,,	240
16	30	M	AF	79	+	+	,,	480
17	58	F	AF	84	–	+	,,	240
18	57	M	AF	130	+	+	Metoprolol	100
19	57	M	AF	110	–	–	Oxprenolol	240
20	44	M	AF	83	+	+	Propranolol	720
21	14	M	SR	76	–	–	Metoprolol	50
22	48	M	SR	67	+	+	,,	200
23	38	F	SR	69	–	+	Oxprenolol	480
24	31	F	SR	74	+	+	,,	60
25	34	M	SR	55	–	+	Propranolol	240
26	57	M	SR	73	+	+	,,	200
27	17	M	SR	70	+	+	,,	120
28	63	F	SR	71	–	–	,,	120
29	56	F	SR	77	–	+	,,	240
30	58	M	SR	56	–	–	,,	120



A2 - O : Rapid Relaxation Period (RRP)
A2 - Mo : Isovolumic Relaxation Period (IRP)
Mo - O : Active Suction Period (ASD)
O - F : Slow Relaxation Period (SRP)
Mo - F : Rapid Filling Period (RFP)

Fig. 1 *Simultaneous recording of phonocardiogram (phono), electrocardiogram (ECG), apexcardiogram (apex), and echocardiogram (echo) in a patient with hypertrophic cardiomyopathy. Diagram shows the diastolic time intervals measured. A_2, aortic component of second heart sound; Mo, mitral valve opening. O and F points of the apexcardiogram.*

were made only on technically satisfactory recordings.

The equipment used was the model VR-12 simultrace system (Electronics for Medicine). This is a multichannel physiological recording system designed for high resolution recording of a variety of signals, including echocardiograms. The photographic tracings were recorded during relaxed expiratory apnoea at a paper speed of 100 mm per second with 0·02 second time lines. This allows a maximal attainable limit for measuring diastolic time intervals of 5 ms. Since the timing of different events during diastole was measured this method is reproducible.[20]

APEXCARDIOGRAM AND PHONOCARDIOGRAM

The apexcardiogram and phonocardiogram (from the apex) were obtained from a single E for M model PSA–23 crystal transducer with infinite time constant. It was positioned at the point where the apexcardiogram was similar to the left ventricular pressure curve and usually coincided with the point of maximal cardiac impulse. The transducer was held in place by an adjustable elastic strap. The model V–2207 phonocardiograph amplifier permitted separate frequency-selective amplification and display of the apexcardiogram with a frequency response of 0·1 to 30 Hz and the phonocardiogram with a band of interest of 50 to 1000 Hz. In this fashion the apexcardiogram was recorded simultaneously with the phonocardiogram from the same site.

During the examination of each patient a second phonocardiogram was obtained from the base of the heart using a second crystal transducer simultaneously with the carotid pulse in order to define accurately the aortic component of the second heart sound.

ECHOCARDIOGRAM

The echocardiogram was obtained simultaneously with the apexcardiogram, phonocardiogram, and electrocardiogram using the E for M model V-3280 module and a 1·25 cm diameter, 2·25 MHz transducer. The system provided a pulse repetition rate of 1000 cycles per second, multilevel gain compensation in either continuous time mode, or discrete depth mode with independent adjustments every 2 cm over 24 cm range. Echoes were obtained simultaneously from the interventricular septum, posterior wall, and both the leaflets of the mitral valve paying special attention to the point where the anterior and posterior leaflets separate. During examination gain settings were continuously adjusted with a foot switch until the best available recordings could be made.

From these traces the following variables were measured and are summarised in Fig. 1: (1) heart rate; (2) rapid relaxation period—interval from aortic valve closure (A_2) to the O point of the apexcardiogram; (3) isovolumic relaxation period—interval from A_2 to mitral valve opening (Mo) defined as the point where both the leaflets of the mitral valve separate on the echocardiogram; (4) active suction period—interval from Mo to the O point of the apexcardiogram; (5) rapid filling period—interval from Mo to the F point of the apexcardiogram.

The measurements of timing of different events during diastole were made in milliseconds, from a mean of at least 20 cycles, except for digitising data where two cycles were used; the measurements of dimensions were in centimetres and the velocity in centimetres per second. The results were given as those lying within the range of one standard deviation of the corresponding mean value. The statistical significance of differences between means of normally distributed populations was assessed by Student's t test.

Results

(1) *Heart rate:* the mean heart rate of patients off treatment was 71·6±16·6 beats per minute. Fig. 2 shows that the heart rate decreased significantly after beta blockade in all but four patients. The mean heart rate on beta blockade was 58·1±10·9 beats per minute ($p<0.001$).

(2) *Rapid relaxation period: A_2–O.* The mean rapid relaxation period for all patients was prolonged after beta blockade from 178·0±42·9 to 185·0±47·7 ms (Table 2). Though overall there was an increase of rapid relaxation period reflecting prolonged relaxation after beta blockade, this was not significant ($p>0.15$). As shown in Fig. 3, however, in 19 patients there was a prolongation of rapid relaxation period, in eight patients it was shortened, and it remained unchanged in three.

(3) *Isovolumic relaxation period: A_2–Mo.* Overall the isovolumic relaxation period was shortened in patients with hypertrophic cardiomyopathy after beta adrenergic blocking drugs but this change was also not significant. The mean value off beta blockade was 82·8±27·9 ms which decreased after treatment to 77·0±28·0 ms ($p>0.10$). From the whole group the isovolumic relaxation period, however, was shortened in 16, prolonged in 12, and remained the same in two (Fig. 4 and Table 2).

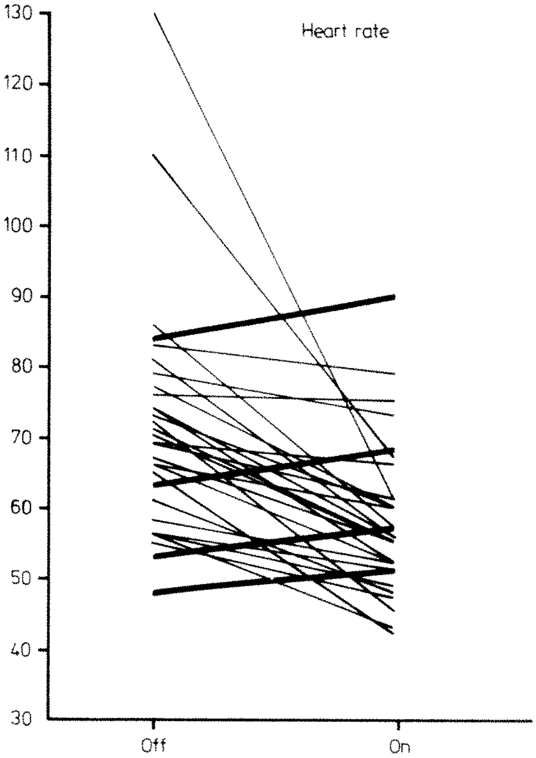


Fig. 2 *The heart rate off and on beta adrenergic blocking drugs. Thin and thick lines represent patients in whom the heart rate decreased and increased, respectively, on beta blockade.*

(4) *Active suction period: Mo–O.* In contrast to rapid relaxation period and isovolumic relaxation period, the mean active suction period was significantly prolonged after treatment when the whole group was considered. The increase was from 95·1±31·3 to 108·1±41·0 ms ($p<0.01$) as shown in Table 2 and Fig. 5. From the whole group, this interval was prolonged in 22, was shortened in seven, and remained the same in one patient.

From the group of 22 patients who had prolongation of the active suction period after beta blockade, 11 had shortening of the isovolumic relaxation period after treatment, nine had prolongation, and two had no change.

(5) *Rapid filling period: Mo–F.* Overall the rapid filling period was significantly prolonged in patients after beta adrenergic blocking drugs (169·7±31·0 to

Table 2 *Behaviour of diastolic time intervals on and off beta blockade in hypertrophic cardiomyopathy*

	Off (ms)	*On (ms)*	*P values**		*Off (ms)*	*On (ms)*
Rapid relaxation period (A_2–O)	178·0±42·9	195·0±47·7	p<0·15	19 prolonged	168·9±41·3	196·0±50·7
				8 shortened	196·8±47·8	158·7±37·3
				3 same	185·0±32·7	185·0±32·7
Isovolumic relaxation period (A_2–Mo)	82·8±27·9	77·0±28·0	p<0.10	12 prolonged	81·2±24·2	99·5±23·1
				16 shortened	86·8±31·4	62·1±21·2
				2 same	60·0±—	60·0±—
Active suction period (Mo–O)	95·1±31·3	108·1±41·0	p<0.01	22 prolonged	90·6±31·1	115·6±43·4
				7 shortened	112·1±29·5	89·2±26·8
				1 same	72·9±—	72·9±—
Rapid filling period (Mo–E)	169·6±31·0	193·5±47·1	p<0.0005	22 prolonged	172·5±33·9	209·7±43·0
				6 shortened	160·8±24·7	143·3±24·6
				2 same	165·0±7·0	165·0±7·0

*p values calculated by Student's t test.

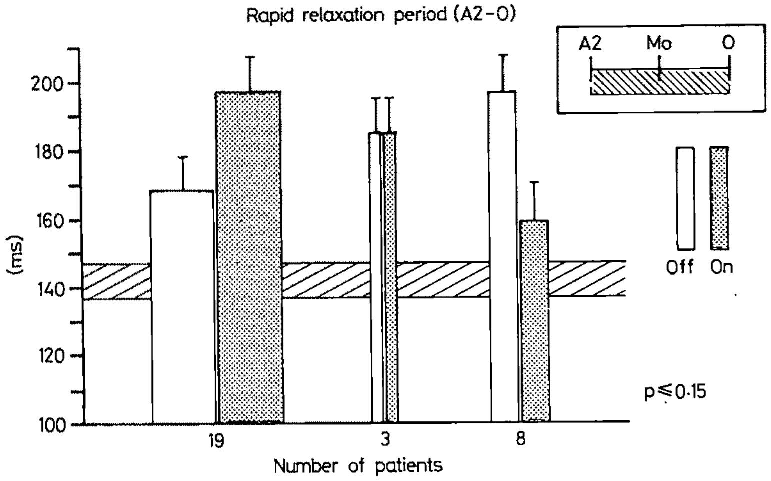


Fig. 3 *Histograms showing the effect of beta blockade on rapid relaxation period (mean ±SD) off treatment (white histograms) and on treatment (stippled histograms). The horizontal bar represents the normal mean value ±SD in normal subjects off beta adrenergic blocking drugs.*

193·5±47·1 ms, p<0·0005). From these 30 patients, in 22 the rapid filling period increased after treatment, in six it was shortened, and in two it remained unchanged (Table 2).

Discussion

The investigation of diastole using simultaneous non-invasive methods such as phonocardiogram, electrocardiogram, left ventricular echocardiogram, and apexcardiogram is possibly at the moment the most effective way to study the events during diastole.

It is possible to identify three important landmarks during the early diastolic period using these techniques: aortic valve closure (A_2), mitral valve opening (Mo), and the O point of the apexcardiogram.

Aortic valve closure indicates the onset of diastole though relaxation has already started at this point. Once the aortic valve has closed there is a rapid fall of left ventricular pressure until the O point of the apexcardiogram (Fig. 1) This interval is the rapid relaxation period and when it is prolonged (as often happens in hypertrophic cardiomyopathy) it reflects a reduced rate of fall of left ventricular pressure.

During this period when there is a gradient cross-over between the left atrium and left ventricle, the mitral valve opens. This period from A_2 to Mo is the isovolumic relaxation period and it depends not only on the rate of fall of left ventricular pressure but also on the left atrial pressure at the time of gradient cross-over between left ventricle and left atrium.

When the mitral valve opens, filling of the left ventricle starts and from this moment onwards the left ventricular pressure is the result of two major interdependent factors: the rate of relaxation and the rate of filling.

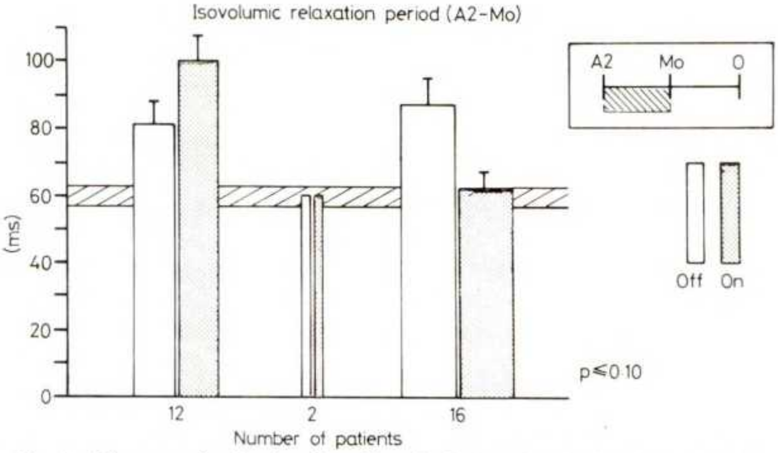


Fig. 4 *Histograms showing the effect of beta blockade on isovolumic relaxation period (mean ±SD) off treatment and on treatment (white and stippled histograms, respectively). The horizontal bar represents the normal mean value ±SD in normal subjects off beta blockade.*

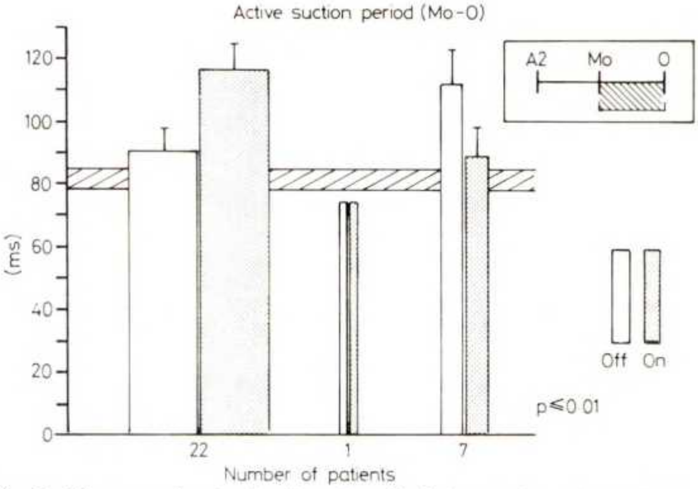


Fig. 5 *Histograms showing the effect of beta blockade on active suction period (mean ±SD) off treatment (white histograms) and on treatment (stippled histograms). The horizontal bar represents again the normal mean value ±SD in normal subjects off beta adrenergic blocking drugs.*

From the mitral valve opening to the O point of the apexcardiogram when the pressure continues to drop (Fig. 1) the rate of relaxation of the left ventricle is greater than the rate of blood filling the left ventricular cavity as a result of which there is a "sucking" effect of the blood coming from the left atrium to the left ventricle. This is the active suction period when most of the left ventricular filling occurs,[21] which goes with a considerable increase in dimension during downstroke of the apexcardiogram[21 22] and rapid thinning of the posterior wall and interventricular septum. Therefore the longer this period is the better will be the left ventricular filling.

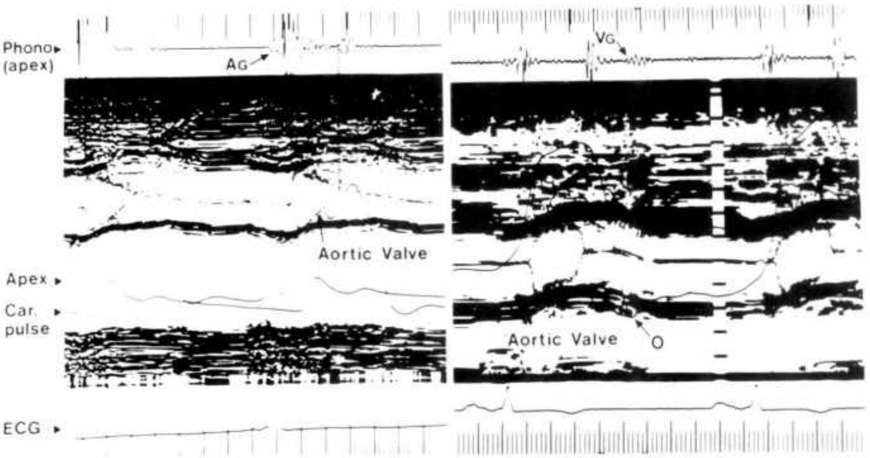
There is controversy about this period especially between those who believe that the relaxation and filling are purely passive processes, determined by venous pressure (vis-a-tergo of Harvey) and those who believe (as this study suggests) that diastolic filling is governed, at least in part, by an active process originating in the ventricular myocardium. This is shown by the fact that the mitral valve opens before minimum ventricular pressure is reached, so that early diastolic filling is associated with a reduction, rather than an increase, in left ventricular pressure. Katz[23] concluded that it reflects a sucking effect of the left ventricle drawing blood into its chamber, and more recently[24-26] further evidence has been produced for such diastolic suction. Hammermeister and Warbasse[27] have shown that during this period (Mo–O), more than 50% of filling is already completed. Thus this period is really the "rapid filling wave" which is not the interval from O to F point of the apexcardiogram as was previously described; it was thought in the pre-echocardiographic era that the O point was coincident with mitral valve opening, since in many cases it corresponded with the opening snap in patients with mitral stenosis.[28]

From the O point to the F point of the apexcardiogram the rate of filling is greater than the rate of relaxation and this is why the left ventricular pressure starts to rise (Fig. 1) though in absolute terms the volume of blood coming to the left ventricle is less than during the active suction period. The interval from mitral valve opening until the F point of the apexcardiogram is defined as the rapid filling period. Thus the O point of the apexcardiogram is the "turning point" where the rate of filling and the rate of relaxation are in equilibrium.

The results of the present work using these techniques suggest that there was no significant prolongation of the rapid relaxation period (Fig. 3) or significant shortening of the isovolumic relaxation period (Fig. 4) after beta blockade. There was, however, a significant increase in the interval from mitral valve opening to the O point of the apexcardiogram as shown in Fig. 5 when most of the left ventricular filling occurs. Prolongation of this period occurred in 22 patients (74%) but it remained the same or was shortened in one (3%) and in seven (23%), respectively. Thus beta blockade is usually valuable in hypertrophic cardiomyopathy since increase in left ventricular filling is achieved at a much lower pressure and this may explain the relief of symptoms. In addition because of this improved early filling, there is less distension of the left atrium, thus possibly preventing the occurrence of atrial fibrillation. The atrial beat also tends to be less powerful after beta blockade.

Shortening of the isovolumic relaxation period possibly contributes to the increase of the Mo–O interval. The former had a variable response after beta blockade, but showed an overall shortening which was not significant. Of 22 patients who had an increased active suction period, 11 had a shortened isovolumic relaxation period. In the remaining 11 it was prolonged or remained unchanged. In addition the increase of active suction period was not directly proportional to the shortening of the isovolumic relaxation period in the 11 patients where this period was shortened after treatment.

Thus, possibly the main reason for prolongation of the Mo–O interval is that the equilibrium point (O point) is reached much later because of relaxation at a much lower pressure as a consequence of which there is increased filling in early diastole. These results confirm the work of de la Calzada *et al.*[15] who have shown acceleration of diastolic closure rate of the



Off treatment (without gallop) On treatment (with gallop)

Fig. 6 *Aortic valve echocardiogram with simultaneous phonocardiogram (phono), apexcardiogram (apex), carotid pulse, and electrocardiogram off and on treatment. Off treatment, as a result of low stroke volume, the aortic leaflets begin to close early while on treatment the leaflets remain widely open throughout systole.*

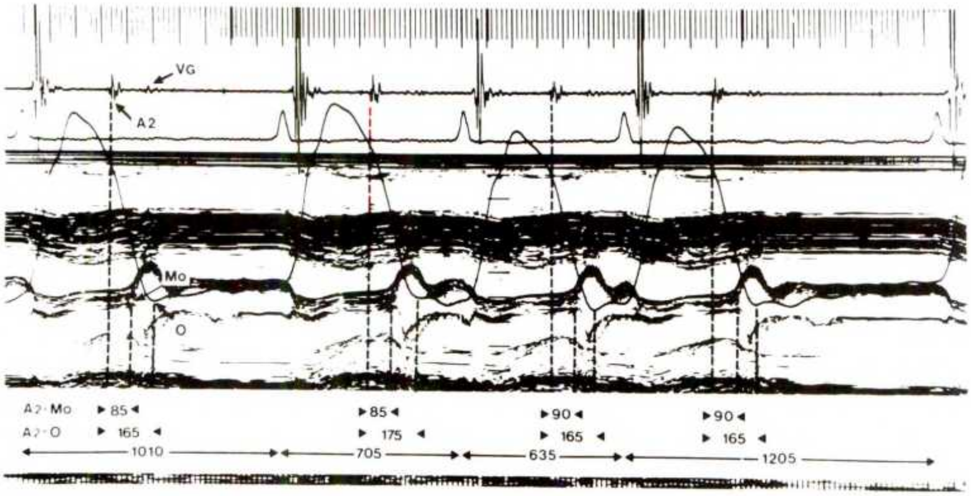

VG
A2
Mo
O
A2·Mo ▸85◂ ▸85◂ ▸90◂ ▸90◂
A2·O ▸ 165 ◂ ▸ 175 ◂ ▸ 165 ◂ ▸ 165 ◂
1010
705
635
1205

Fig. 7 *Patient with hypertrophic cardiomyopathy in atrial fibrillation. The isovolumic relaxation period (A_2–Mo) and the rapid relaxation period (A_2–O) almost remain constant with different RR intervals.*

mitral valve after beta blockade probably related to increased ventricular filling.

The consequence of this increased filling can be seen in Fig. 6 where after treatment there was an increase in stroke volume, as shown by increased aortic valve opening.

This increase in the active suction period was not affected by age, by sex, by the type or amount of the drug, by blood pressure, or by heart rate. This can be seen in Fig. 7 where a patient with hypertrophic cardiomyopathy and in atrial fibrillation with different RR intervals had almost constant rapid relaxation period and isovolumic relaxation period. In this group of 30 patients the coefficient of correlation between the heart rate and the diastolic time intervals in early diastole (A_2–O, A_2–Mo, Mo–O) was extremely low. Nor was this increase of active suction period affected by the presence of a gradient to the outflow tract of the left ventricle.

The effect of beta blockade in lowering the heart rate should not be underestimated because an appreciable amount of filling occurs during the slow relaxation period, diastasis, and the atrial component of diastole which are all related closely to the heart rate. Indeed, clinically there is pronounced deterioration of these patients when they are in atrial fibrillation.

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sage instituted. Adverse effects of bendro-
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nay be precipitated in hepatic cirrhosis.
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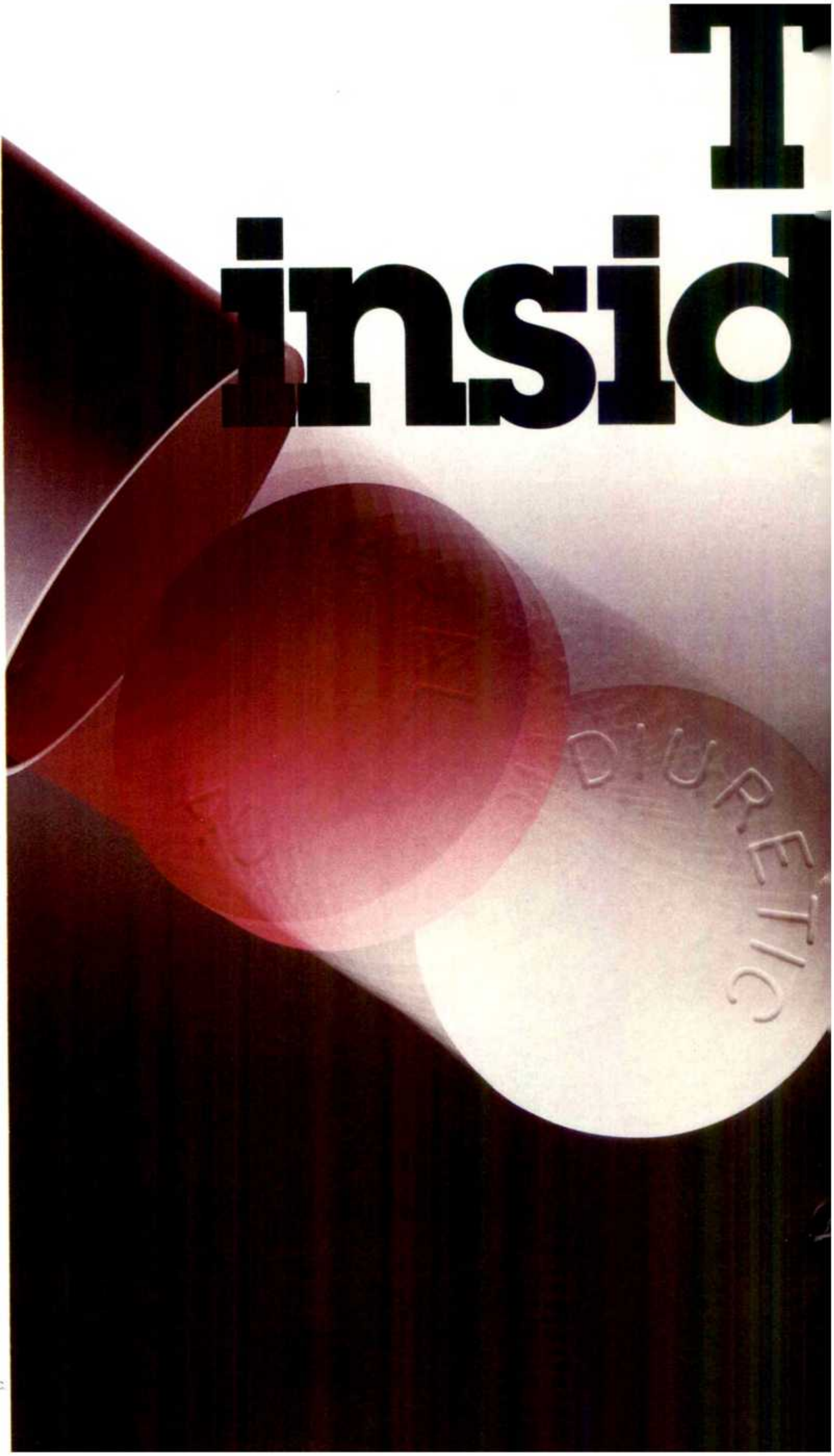

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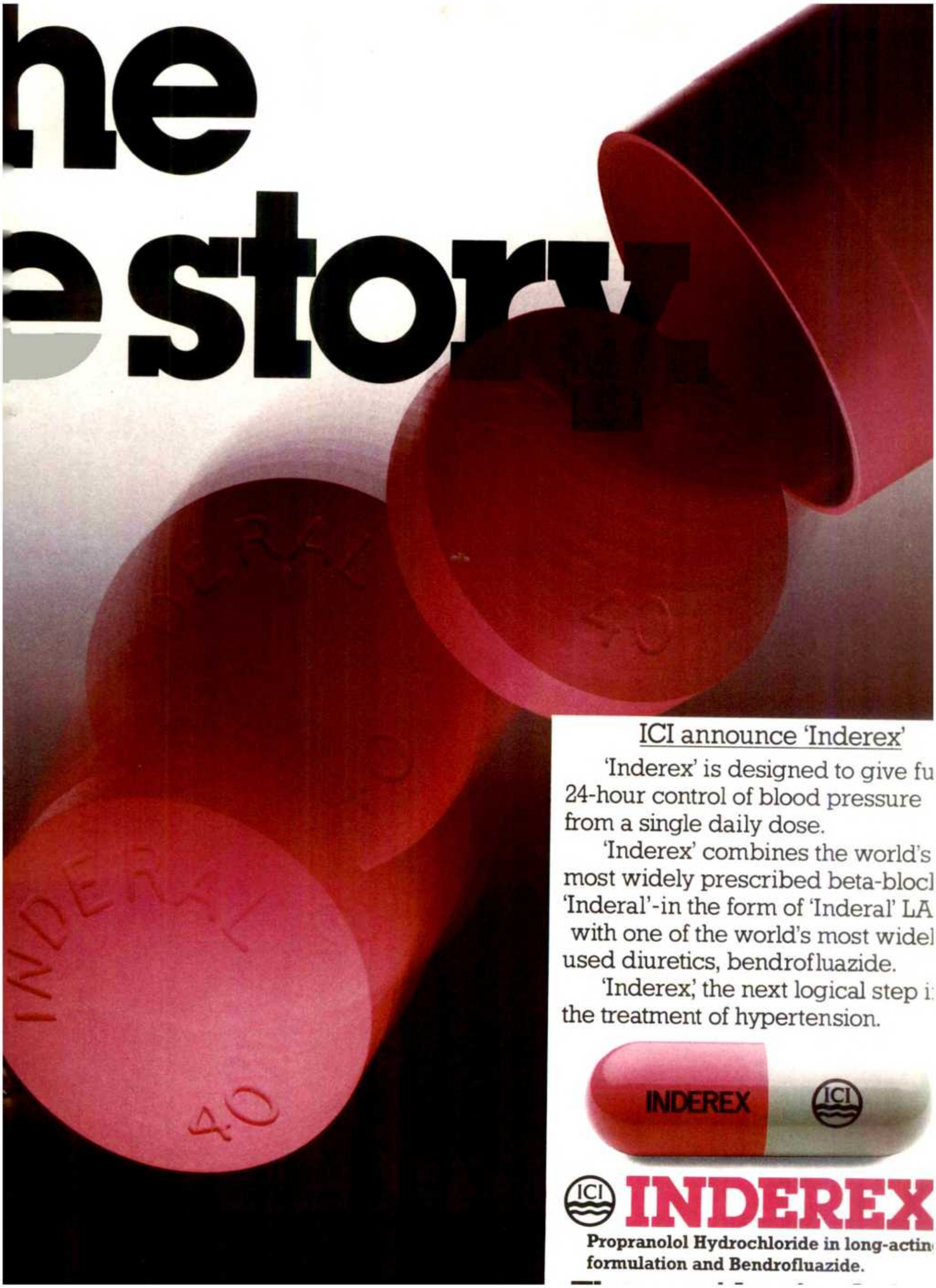

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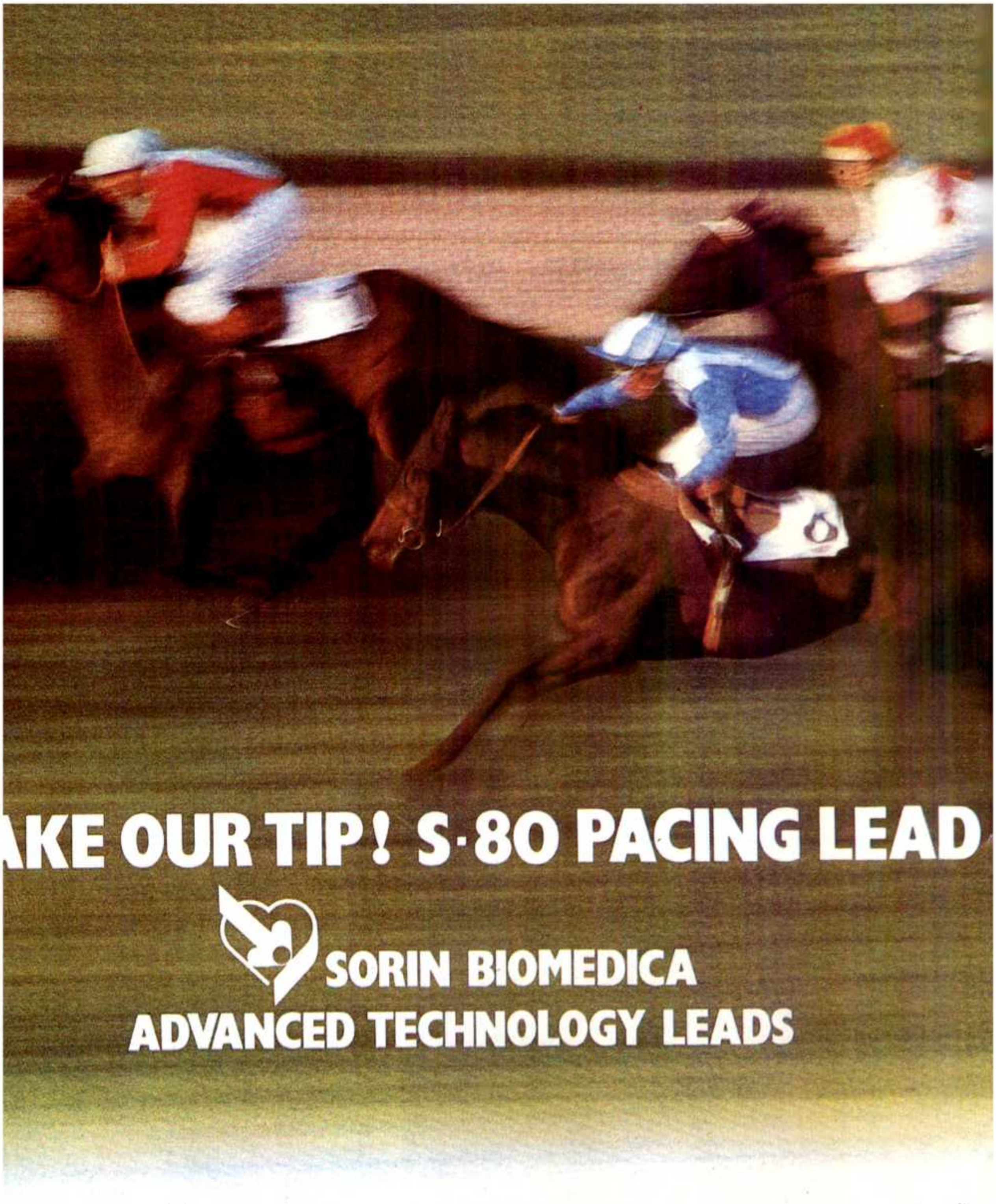

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"Torsade de pointes" tachycardia
Re-entry or focal activity?

C NAUMANN D'ALNONCOURT, W ZIERHUT, B LÜDERITZ

From Department of Internal Medicine, Klinikum Grosshadern, University of Munich, West Germany

SUMMARY Paroxysms of ventricular tachycardia in which the amplitude and the direction of QRS complexes change periodically are defined as "torsade de pointes" tachycardias. The mechanism of this atypical ventricular arrhythmia has not yet been elucidated. The aim of our study was to induce "torsade de pointes" tachycardia experimentally, in order to gain insight into its possible mechanism. The experiments were carried out with isolated porcine hearts, perfused by the Langendorff technique. Epicardial electrocardiograms were recorded by unipolar leads. The specific pattern of "torsade de pointes" tachycardia could be induced by stimulation of the right and left ventricles in phase. From our experimental observations we conclude that a possible cause of "torsade de pointes" tachycardia is the interaction of two ectopic ventricular foci.

Rapid ventricular tachycardias, with periodic change of amplitude and direction of the QRS complexes, are defined as "torsade de pointes" tachycardias.[1] A detailed description of this serious arrhythmia has been given by Dessertenne,[2] who also created the term "torsade de pointes" (twisted tips). The precise mechanism of this atypical ventricular arrhythmia has not been completely clarified. Prolongation of the QT interval and inhomogeneous repolarisation of neighbouring areas of the myocardium are believed to be of major importance for its genesis.[1 3] "Torsade de pointes" has been recognised during hypokalaemia,[4-6] hypomagnesaemia,[7 8] acute ischaemia,[9] myocardial infarction,[10] myocarditis,[1] during the use of various antiarrhythmic agents, for example quinidine,[11] lignocaine,[1] mexiletine,[12] disopyramide,[13 14] and could be initiated by electrical ventricular stimulation.[15] Thus, aetiology of this rhythm disorder is diverse; its characteristic electrocardiographic appearance, however, suggests a specific mechanism.

The aim of our study was to induce "torsade de pointes" tachycardias experimentally in order to gain insight into its possible mechanism.

Methods

The experiments were carried out in isolated pig hearts (n=7). The animals (weight 20±1 kg) were anaesthetised by intravenous injection of sodium pentobarbitone (15 mg/kg). After intubation and artificial respiration the thorax was opened by a midsternal incision and the heart was rapidly removed and fixed to a heart lung machine where it was perfused with the blood of the same pig using the Langendorff technique.[16] The temperature was 37°C, and the coronary flow was set at 200 ml/min. The hearts were paced electrically from the epicardium with two independent stimulation generators at one and a half times the diastolic threshold. Unipolar electrocardiograms were recorded by means of non polarisable cotton wick electrodes from the epicardium and were recorded on an Elema ink writer (Fig. 1).

Results

If paced from the right ventricle the electrocardiogram recorded within the area of the left anterior descending artery showed a positive deflection (R wave); if paced from the left ventricle the main axis of the QRS complex at the same recording point became negative (S wave) (Fig. 2). If the stimulation was performed from both the right and the left ventricles the resulting QRS deflection could be made zero if there was an appropriate interval between both stimuli. With the right ventricle stimulated at a constant rate (245/min) and the interval of the second stimulus (left ventricle) changed stepwise, the amplitude of the QRS could be adjusted between the maximum negative S wave and the maximum positive R wave. By

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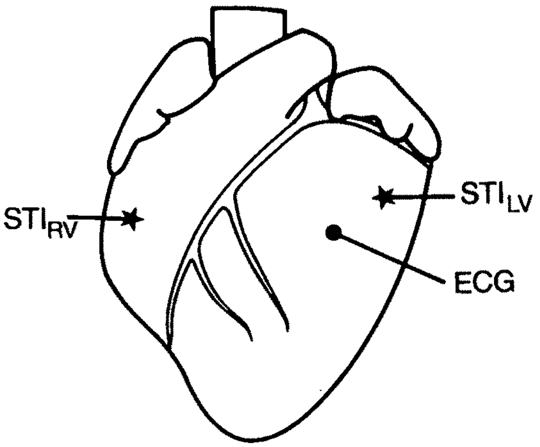

Fig. 1

Fig. 1 *Isolated pig heart perfused by the Langendorff method. Arrangement of the stimulation and recording electrodes.* STI_{RV}, *site of stimulation on the right ventricle;* STI_{LV}, *site of stimulation on the left ventricle; ECG, recording point on the left ventricle.*

Fig. 2 *Electrocardiograms during stimulation of the right ventricle or the left ventricle. (a) If stimulation is performed to the right ventricle the electrocardiogram shows an R wave; (b) if stimulation is performed to the left ventricle the electrocardiogram shows an S wave.*

Fig. 3 *Electrocardiogram during stimulation of the right and the left ventricle. If the left ventricle is paced at a constant rate (cycle length CL: 245 ms) and the right ventricle is paced at a similar but periodically changing rate (CL: 230 to 260 ms) the electrocardiographic pattern of "torsade de pointes" occurs.*

Fig. 4 *After inducing ventricular tachycardia by occlusion of the left anterior descending coronary artery the electrocardiographic pattern of "torsade de pointes" could be generated by pacing the right ventricle at a similar but periodically changing rate. STI, start of stimulation of the right ventricle.*

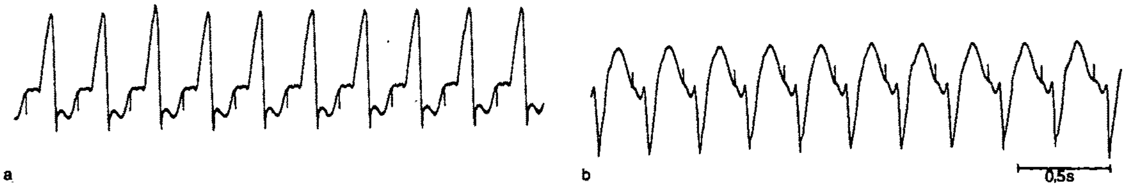

Fig. 2

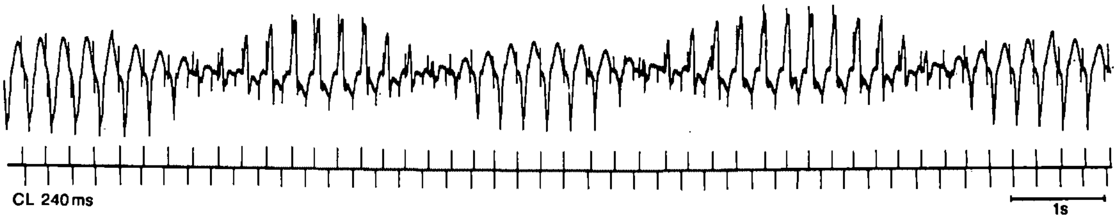

Fig. 3

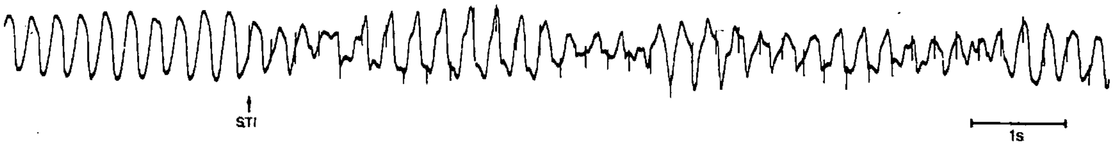

Fig. 4

continuous prolongation of the coupling interval of the second stimulus from the basic stimulus a gradual decrease of the amplitude of the R wave occurred until it disappeared and then the QRS deflection became negative, increasing until it reached a maximum negative S wave (Fig. 3). If the interval was then shortened the amplitude of the S wave decreased, became zero, and changed again into a positive R wave.

In another series of experiments (n=4) the left anterior descending artery was occluded to produce a stable ventricular tachycardia and then only one pacemaker, stimulating the heart from the right ventricle, was necessary to generate the electrocardiographic pattern of "torsade de pointes". The pacing rate was set at the heart rate and by slowly shortening and lengthening the stimulation interval the electrocardiographic pattern shown in Fig. 4 was recorded.

Discussion

Our results suggest that "torsade de pointes" tachycardias are based on focal impulse formation and on the interference of two separated foci with two different rates. If these foci are located in the right and in the left ventricle, the electrocardiogram shows either left bundle-branch block or right bundle-branch block. If both foci are active the resulting electrocardiogram represents the sum of both these electrocardiograms. If the impulse spreads from the left ventricle over the heart and the second focus in the right ventricle accelerates increasingly, the electrocardiogram gradually changes from the right bundle-branch block pattern to the left bundle-branch block pattern: "torsade de pointes" occurs.

Others favour the idea of a re-entry mechanism causing "torsade de pointes" tachycardia[17-19] and another possibility is that the tachycardia—beat by beat—originates from a point which slowly moves back and forwards between two regions of the heart, for instance the left and the right ventricle, but no experimental evidence or models have been produced to support these theories.

Our data do not rule out other possibilities but in our opinion there are more arguments for a bifocal genesis than for a re-entrant mechanism. "Torsade de pointes" tachycardias often occur when the excitability of the heart is increased, for example in hypokalaemia, in acute ischaemia, and in myocarditis. Under these conditions abnormal impulse formation could well originate from Purkinje fibres which extend over the whole heart and could set the stage for multifocal activity. The ineffectiveness of lignocaine-like substances in the treatment of "torsade de pointes" fits well with the assumption of abnormal impulse formation in Purkinje fibres, because this type of activity originates from fibres depolarised into a potential range where the fast channel is already inactivated.[20] Furthermore, the frequent observation of a period of bradycardia before the start of a "torsade de pointes" tachycardia argues in favour of focal activity. The usual occurrence of multiform extrasystoles—often in the opposite direction to the QRS complexes—just before spontaneous "torsade de pointes" tachycardias start[1 3 21] also suggests a bifocal genesis for this arrhythmia. Lastly, as long as there is no contraindication, overdrive suppression by cardiac pacing appears to be the treatment of choice for "torsade de pointes" tachycardia.[1 13 18] and its effectiveness again supports our hypothesis of bifocal activity, which was originally advanced by Dessertenne in 1966[2] as the cause of this arrhythmia.

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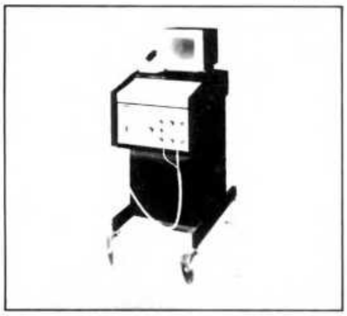

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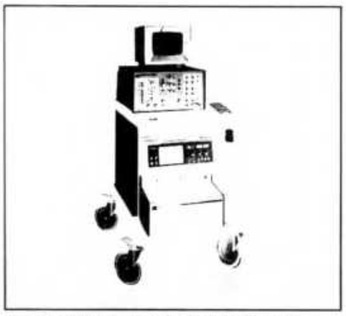

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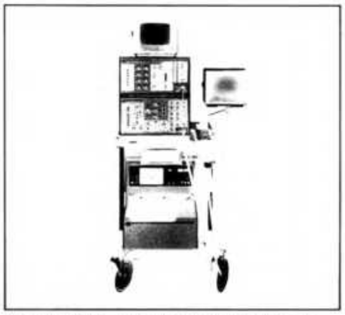

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Significance of complete right bundle-branch block when an isolated finding

An echocardiographic study

MARK DANCY,* GRAHAM LEECH, AUBREY LEATHAM

From the Cardiac Department, St George's Hospital, London

SUMMARY Twenty-seven patients with complete right bundle-branch block as the only abnormal finding were studied using high speed M-mode echocardiography to determine the effect of the electrical delay on the mechanical events of right ventricular systole. Pulmonary valve opening (PVOm) was delayed in all cases. In some the delay was mainly between mitral valve closure (MVC) and tricuspid valve closure (TVC), and this was designated proximal block. In the others the main delay was between tricuspid valve closure and pulmonary valve opening and this was designated distal block. The patients were divided into those with proximal and those with distal block by calculating the ratio TVC-PVOm/MVC-TVC. Twelve out of 13 of those with distal delay but only one out of 14 of those with proximal delay had episodes of syncope or near syncope. These results are consistent with previous theories about the pathophysiology of right bundle-branch block. Echocardiography may offer a non-invasive method to estimate the prognosis in isolated right bundle-branch block.

When complete bundle-branch block is discovered as an isolated finding in a patient who has no other evidence of heart disease, the long-term prognosis is difficult to assess, and this is particularly important in aviation and insurance medicine. The finding of right bundle-branch block is usually unimportant,[1] but in occasional patients it is an early sign of diffuse conducting tissue disease, cardiomyopathy, or coronary artery disease. There is at present no reliable way of distinguishing this important second group of patients with underlying or progressive disease.

It is now fairly well established that there are two forms of right bundle-branch block: one in which there is interruption of the main right branch of the bundle of His, termed proximal block, and the other in which the terminal ramifications of the right bundle are affected, termed distal or arborisation block.[2-4] Brooks *et al.*[5] suggested that patients with right bundle-branch block could be divided into those with proximal block and those with distal block by timing right sided systolic events using echophonocardiography; these authors speculated that there might be a difference in prognosis between the two groups, proximal being relatively isolated and benign, but distal being associated with diffuse disease which was likely to be more widespread and progressive. In the group thought to have proximal block, they found that the right sided delay was confined to prolongation of the time interval between mitral valve closure and tricuspid valve closure on the echocardiogram. In the group thought to have distal block the delay was mainly between tricuspid valve closure and pulmonary valve opening.

In order to test the hypothesis that proximal block is usually a benign condition, and that distal block is more likely to be associated with more widespread disease, we measured these time intervals in patients in whom right bundle-branch block was an isolated finding at a routine examination, and compared them with the results from an otherwise identical group of patients with right bundle-branch block who had a history of syncope or near syncope.

Patients and method

The 27 patients included in this study all had basic sinus rhythm with typical complete right bundle-branch block at the time of study. None had evidence of any other cardiac disorder on radiographic, echocardiographic, or electrocardiographic grounds.

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In particular there was no electrocardiographic evidence of left sided conduction disease (normal PR interval and QRS axis). In 14 patients the right bundle-branch block had been discovered at a routine examination (for example for a pilot's licence or insurance) and they were free of symptoms. The remaining 13 patients had suffered attacks of syncope or near syncope though they were otherwise symptom free. Eleven of the 13 had had documented episodes of complete heart block. Eight of them had had demand pacemakers fitted. Of those with pacemakers, three were in sinus rhythm inhibiting the pacemaker at the time of the study, and in five sinus rhythm was induced by external inhibition of the pacemaker using surface electrodes and an impulse of 100/min from an external pacing unit.

There was no significant difference in age between those patients with symptoms (mean 66 years, range 42 to 83) and those without (mean 60 years, range 42 to 69). The results were compared with those from a group of 63 normal subjects who were younger than the patients, with a mean age of 33 years (range 19 to 56 years).

Echocardiograms were recorded on a Smith Kline Ultrasonoscope using a 2·25 MHz focused transducer with pulse repetition frequency increased to 2000/s. The output was displayed on a Cambridge 6 channel recorder with maximum paper speed increased to 200 mm/s. Magnified recordings were made of the mitral, tricuspid, and pulmonary valves, together with a high frequency phonocardiogram from the fourth left intercostal space and the standard electrocardiographic lead showing the earliest onset of QRS. The technique and details of measurement have been fully described elsewhere.[5] Measurements were made from Q to mitral valve closure (MVC), Q to tricuspid valve closure (TVC), and Q to pulmonary valve opening (PVOm) (maximum pulmonary valve opening was measured instead of the onset of pulmonary valve opening as it is a reproducible event that can be measured with great accuracy). From these results the time intervals MVC to TVC and TVC to PVOm were calculated.

Statistical analysis was carried out using Student's unpaired t test unless otherwise stated.

Results

Mean time interval measurements for the two patient groups and the normal subjects are shown in the Table. The results for individual subjects are shown graphically in Fig 1; values of MVC-TVC (interrupted line) and TVC-PVOm (solid line) for each subject are indicated with reference to the time of TVC. Heavy lines under each patient group show mean values for that group and only the mean values are given for the 63 normal subjects.

Table *Mean time intervals in 63 normal subjects, 14 patients with right bundle-branch block and no symptoms, and 13 patients with right bundle-branch block and syncope (p values refer to comparisons between normals and patient groups)*

Subjects	*No.*	*Q-MVC*	*MVC-TVC*	*TVC-PVOm*
Normal	63	55±11	34±10·5	39±12
Without symptoms	14	57±22†	58±11**	53±12*
With symptoms	13	59±15†	33±18†	95±32**

All figures in ms±SD.
†NS;
*p<0·005;
**p<0·001.
Q-MVC, interval from onset of QRS to mitral valve closure; MVC-TVC, interval from mitral to tricuspid valve closure; TVC-PVOm, interval from tricuspid valve closure to maximal pulmonary valve opening.

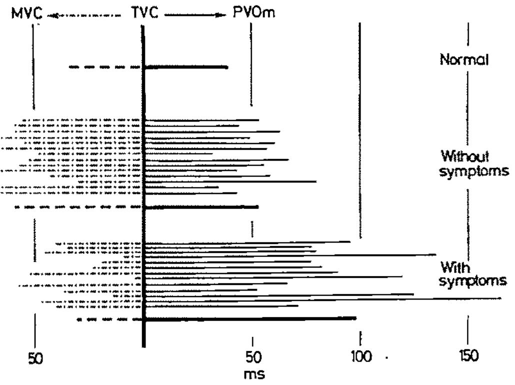

Fig. 1 *Values of the intervals of MVC-TVC (interrupted horizontal lines to the left of the vertical line), and TVC-PVOm (solid horizontal lines to the right of the vertical line) displayed in relation to the time of tricuspid valve closure (the vertical line). Beneath each patient group is the mean (thicker lines).*

MVC TO TVC INTERVAL

In all but one of the 14 symptom-free patients with right bundle-branch block the time interval from mitral valve closure to tricuspid valve closure was longer than the mean of the normal subjects. This had been strongly suspected clinically in most because of wide splitting of the first heart sound. In addition, the mean value was significantly prolonged in these symptom-free patients when compared either with those with symptoms (p<0·001) or with normal subjects (p<0·001).

In the patients with syncope the mean interval was not prolonged, but there was considerable individual variation (Fig 2).

TVC TO PVOm INTERVAL

In the symptom-free patients the time interval from tricuspid valve closure to pulmonary valve opening was within the normal range in 10, but in four it was

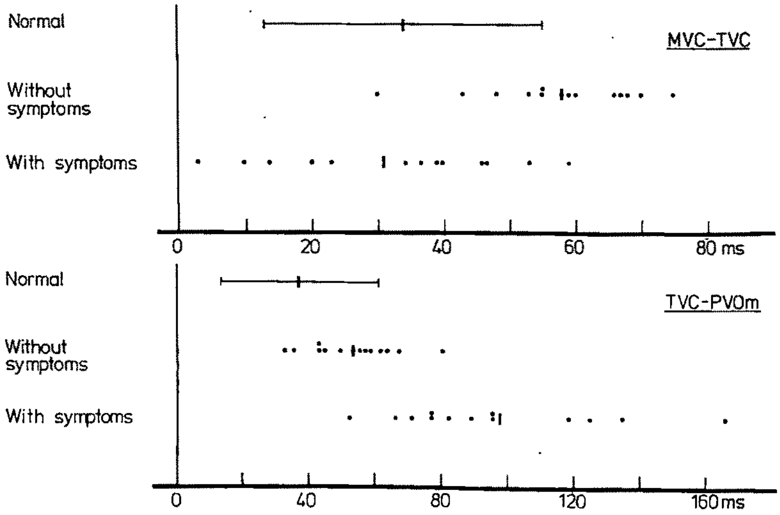

Fig. 2 *Individual values of MVC-TVC and TVC-PVOm shown in comparison with the range of 63 normal subjects (mean ± 2 SD).*

slightly prolonged, and the mean was slightly greater than normal ($p<0{\cdot}005$). It should be noted in this respect that both groups of patients were significantly older than the normal subjects. In all but one of the patients with syncope, TVC-PVOm was abnormally prolonged, and was usually greatly prolonged. Mean TVC-PVOm was significantly increased in these patients both when compared with the normal subjects ($p<0{\cdot}001$) as well as with the symptom-free group ($p<0{\cdot}001$).

RATIO OF TVC-PVOm/MVC-TVC (Fig 3)

By combining the two measurements a greater separation was achieved between the patients with symptoms and those without. This ratio was greater than the arbitrary value 1·4 in all but one of the patients with syncope, and less than 1·4 in all but one of the symptomless patients with right bundle-branch block ($p<0{\cdot}001$ by χ^2 test).

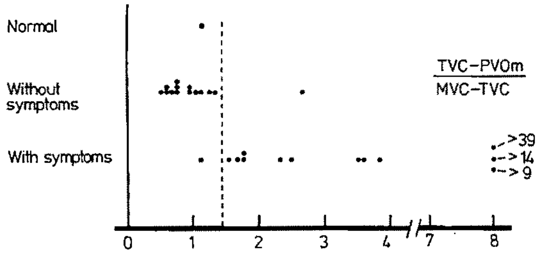

Fig. 3 *Ratio of TVC-PVOm/MVC-TVC for all the patients. An arbitrary line is drawn at 1·4. Those patients with values below this are considered to have proximal block, whereas those with values above are considered to have distal block.*

Discussion

There is considerable evidence from physiological studies to suggest that the electrocardiographic pattern of right bundle-branch block is identical whether the interruption is in the proximal or distal portions of the right His-Purkinje network.[6-9] Anatomically, the right bundle comprises a single group of fibres which arborises only at the periphery. Interruption of the proximal portion is therefore likely to cause delay in the onset of right ventricular contraction, but, assuming the distal network is intact, contraction should then proceed normally. On the other hand, disease affecting the peripheral branches, but not the proximal bundle, ought to cause asynchronous contraction, slowing the overall rate of rise of pressure without delaying its onset. In both cases the effect would be to delay the opening and closure of the pulmonary valve. Generalised disease of the right conduction system should cause proximal and distal delays in the same patient.

Animal studies with selective interruption of the proximal[6 7] and distal[8 9] fibres have confirmed these suggestions. In man the relation between the anatomical site of interruption of the right bundle and the consequent electrical delays have been studied by epicardial isochrone mapping during surgical procedures that produced right bundle-branch block.[10] Proximal interruption produced similar delays in activation of all parts of the right ventricle, whereas distal interruption slowed the rate of propagation of the depolarisation wave.

Alterations in the sequence of events during systole are reflected in the heart sounds. Indeed, a study of the sequence of the aortic and pulmonary components of the second heart sound provided the first clue that the early electrocardiographers had confused the electrocardiographic patterns of right and left bundle-branch block which had been derived from studies on dogs.[11] Abnormally wide splitting of the first heart sound, attributed to delay of tricuspid valve closure, was found to be a feature of apparently isolated right bundle-branch block, and was also found in other circumstances with delayed onset of right ventricular contraction, such as with pacing from the left ventricle or with ectopic beats of left ventricular origin.[12] Echophonocardiographic studies in Ebstein's anomaly, in which the right bundle comprises only a short proximal group of fibres, showed a striking delay of the tricuspid component of the first heart sound.[13] It was pointed out, however, that the onset right ventricular systole was not invariably delayed in right bundle-branch block[4] and an echocardiographic study confirmed that in some instances right bundle-branch block did not cause delay of tricuspid valve closure.[5] These findings strongly suggested that in such cases the delay in activation was confined to the peripheral fibres. It was also noted that most of the patients in this group had cardiac abnormalities in addition to right bundle-branch block; indeed, peripheral delay would be expected with myocardial disease, myocardial infarction, and particularly idiopathic bundle-branch fibrosis which is the commonest cause of complete heart block.[14–16]

There is therefore substantial evidence that there are two pathologically distinct forms of isolated right bundle-branch block. Proximal block, caused by a single localised lesion, may be the underlying pathology in the majority of cases of isolated right bundle-branch block which statistically have an excellent prognosis.[1] Distal block, where the underlying lesion is more diffuse, may be evidence of the progressive disease seen in a minority of patients. The present study was designed to show whether the position of the block could be predicted by echophonocardiographic timing studies, and whether this had any prognostic relevance. For this purpose, delay of tricuspid valve closure relative to mitral valve closure was regarded as evidence of proximal block, and delay between tricuspid valve closure and pulmonary valve opening as distal block.

The results for the symptom-free patients with right bundle-branch block showed that the mean value of MVC-TVC was significantly prolonged ($p<0{\cdot}005$ compared both with normal subjects and with patients with symptoms) and in nine cases was outside the normal range. TVC-PVOm, however, was normal in the majority, though in four it was slightly prolonged. The patients with a history of syncope, whose electrocardiograms were indistinguishable from those of the symptom-free patients with right bundle-branch block, had striking prolongation of the mean TVC-PVOm interval, which was 2·4 times that of the normal subjects ($p<0{\cdot}001$ compared with normal subjects and symptom-free patients). Most showed no delay of tricuspid valve closure, suggesting that the proximal portion of the right bundle was intact, but in some the interval from mitral to tricuspid valve closure was also prolonged, suggesting that there was generalised disease affecting both proximal and distal regions.

Although there was some overlap of measured values for individuals in the two patient groups, this was reduced by expressing the intervals in the form of ratios (Fig. 3). An arbitrary division set at 1·4 for the ratio TVC-PVOm/MVC-TVC gave optimal separation, leaving only one symptom-free patient in the "distal section" and one patient with symptoms in the "proximal section".

Thus, the evidence for the separation of right bundle-branch block into proximal and distal varieties is based on electrophysiological, anatomical, and pathological findings, and we believe that it is possible to place patients in one of these two groups by means of echocardiography, or even by simple auscultation in many cases. Though the number of patients so far studied is small, this seems a promising technique for assessing the prognostic significance of right bundle-branch block. Only a long-term follow-up of patients with isolated right bundle-branch block will disclose whether or not distal block is more likely to be associated with progressive pathology.

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M-mode echocardiographic features of endomyocardial fibrosis

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SUMMARY M-mode echocardiographic findings are described in 21 patients with endomyocardial fibrosis. Features associated with right ventricular endomyocardial fibrosis include: (i) exaggerated motion and thickening of the anterior right ventricular wall; (ii) increased right ventricular end-diastolic dimension; and (iii) paradoxical septal motion.

Pericardial effusion (viz an echo-free space behind the posterior left ventricular wall) was shown in three patients. The tricuspid valve was easily recorded in all. Six patients with left ventricular endomyocardial fibrosis had diminished left ventricular end-diastolic dimension. Three had echo features of pulmonary hypertension (viz reduced e–f slope, absent a wave in sinus rhythm, and systolic notching of the pulmonary valve echogram). Fine fluttering of the anterior mitral valve and tricuspid valve echo was observed in two patients (one of whom was in sinus rhythm) with biventricular endomyocardial fibrosis, and no angiographic evidence of aortic regurgitation.

Endomyocardial fibrosis, a form of obliterative cardiomyopathy, is one of the commonest forms of heart disease in Nigeria[1 2] and other developing countries in Africa[3 4] south of the Sahara. The published reports abound in information on the clinical,[5 6] haemodynamic,[7 8] angiographic,[9 10] and pathological[11 12] features of endomyocardial fibrosis. Information is, however, scanty and sketchy on the echocardiographic features.[10 13]

While the clinical diagnosis of advanced right ventricular or biventricular endomyocardial fibrosis is easy and straightforward, difficulties often arise in mild to moderate cases, when it may be difficult to distinguish at the bedside between endomyocardial fibrosis, rheumatic valvular disease, constrictive pericarditis, and congestive cardiomyopathy.[14] If characteristic echocardiographic patterns of endomyocardial fibrosis can be defined, this would offer a useful non-invasive diagnostic tool in the hands of clinicians, obviating the need for cardiac catheterisation, with its attendant risks. This is a consideration of great importance, especially since the role of surgery in this disease is not yet clearly defined.

We have studied 21 patients with endomyocardial fibrosis by M-mode echocardiography, and our observations form the basis of this paper.

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Subjects and methods

There were 10 male and 11 female patients, whose ages ranged from 6 years to 70 years. They were referred to the Lagos University Teaching Hospital with diagnoses varying from puerperal cardiomyopathy, endomyocardial fibrosis, ascites of unknown cause, unexplained cardiomegaly, to pericardial effusion. Each had an examination on electrocardiogram and a chest x-ray film. Ultrasound examination was carried out using standard techniques, with an SKI Ekoline 20A Ultrasonograph and a Cambridge strip-chart recorder. A 2·25 MHz transducer with a repetition rate of 1000 impulses/s was placed in the left parasternal position, with the patient supine.

Fifteen patients had cardiac catheterisation and angiocardiography, 10 before and five after the echocardiographic examination. In two patients, phonocardiograms were recorded, and aortic root angiography carried out. One patient, who died, came to necropsy.

For comparison, two patients with massive ascites resulting from portal hypertension, two with constrictive pericarditis, and one with tricuspid stenosis, all with clinical appearances similar to endomyocardial fibrosis, were also studied echocardiographically.

Results

Nineteen patients presented with the characteristic clinical picture of right ventricular endomyocardial fibrosis, namely, raised jugular venous pressure, massive ascites, and minimal pedal oedema. Two presented with only mild to moderate ascites. One, a 10 year old boy, had unexplained cardiomegaly. Twelve had clinical evidence of left as well as right heart failure, with a pansystolic murmur of mitral regurgitation. Fifteen patients had clinical evidence of tricuspid regurgitation. An early diastolic murmur was heard in two patients. The radiological and electrocardiographic findings were compatible with the clinical diagnosis of endomyocardial fibrosis. Eighteen were in sinus rhythm and three in atrial fibrillation. There was no left bundle-branch block. The haemodynamic and angiographic study indicated that nine had right ventricular, and six had biventricular endomyocardial fibrosis. Five patients were studied echocardiographically before being subjected to cardiac catheterisation. Of these, two who had aortic root angiograms had no evidence of aortic regurgitation.

The following echocardiographic features were common to all 21 patients.

(1) Increased right ventricular dimension (mean 47 mm; SD 11 mm: normal range 7 to 23 mm) (Table), (Figs. 1 and 2).

(2) Paradoxical septal motion (Fig. 1).

(3) Thickening of the right ventricular anterior wall (mean 9 mm; SD 2 mm: normal < 5 mm), with increased right ventricular anterior wall motion (Fig. 3).

(4) Easily recordable tricuspid valve (Fig. 4). These features were associated with right ventricular involvement. Other features found associated with right sided endomyocardial fibrosis were as follows: (a) Two patients (each with an early diastolic murmur) had fine fluttering of the anterior tricuspid valve leaflet (Fig. 4) (one of these patients was in sinus rhythm); (b) three patients had posterior pericardial effusion (Fig. 5). Features associated with left ventricular endomyocardial fibrosis were as follows: (a) Reduced left ventricular dimension (mean 24 mm; SD 6 mm: normal range 35–56 mm) (Fig. 5), Table). This was found in all 12 patients with biventricular endomyocardial fibrosis. (b) Two patients, who had early diastolic murmur, had fine fluttering of the anterior mitral valve leaflet (Fig. 6). One of these patients was in sinus rhythm. Two other patients in atrial fibrillation who had anterior mitral valve fluttering did not have an early diastolic murmur. (c) Five patients had left atrial enlargement, and (d) three of them showed echocardiographic features of pulmonary hypertension, viz reduced e–f slope, absent a

Table *Clinical, echocardiographic, and haemodynamic data in 21 patients with endomyocardial fibrosis*

No.	*Age (y)*	*Sex*	*Echocardiographic data*			*Haemodynamic data*		*Clinical data*				*EMF involvement (ventricle)*
			RVEDD (mm)	*EDARVWT (mm)*	*LVEDD (mm)*	*RVEDP (mmHg)*	*LVEDP (mmHg)*	*MR*	*TR*	*ECG*	*EDM*	
1	25	F	40	7	34	18–19	15–20	+	+	AF	+	R+L
2	13	F	38	13	32	13–16	15–18	+	+	SR	–	R+L
3	6	M	70	10	19	—	—	+	+	SR	–	R+L
4	32	F	37	10	24	—	—	+	+	SR	–	R+L
5	21	F	37	8	50	12–17	6–10	–	–	SR	–	R
6	56	F	45	9	45	15–20	0– 3	–	+	SR	–	R
7	23	M	46	7	36	18–21	11–12	–	–	SR	–	R
8	50	F	59	7	30	—	—	+	+	SR	–	R+L
9	10	M	50	12	55	16–22	9–12	–	+	SR	–	R
10	19	F	40	6	37	10–15	6–10	–	+	SR	–	R
11	25	F	62	14	22	17–19	20–24	+	+	SR	–	R+L
12	21	M	34	6	42	16–18	0– 6	–	–	SR	–	R
13	64	F	50	10	30	—	—	+	+	SR	–	R+L
14	21	M	47	8	15	—	—	+	–	SR	–	R+L
15	45	M	38	10	50	20–23	6– 7	–	+	AF	–	R
16	22	M	60	7	20	21–22	23–27	+	+	SR	–	R+L
17	15	M	54	12	40	18–22	10–12	–	+	SR	–	R
18	13	F	30	9	38	12–14	9–12	–	–	SR	–	R
19	45	M	56	6	21	17–25	16–20	+	+	SR	+	R+L
20	70	F	35	9	27	—	—	+	–	AF	–	R+L
21	16	M	58	11	19	21–24	18–22	+	+	SR	–	R+L

RVEDD, right ventricular end-diastolic dimension; EDARVWT, end-diastolic anterior right ventricular wall thickness; LVEDD, left ventricular end-diastolic dimension; RVEDP, right ventricular end-diastolic pressure; LVEDP, left ventricular end-diastolic pressure; MR, mitral regurgitation; TR, tricuspid regurgitation; AF, atrial fibrillation; SR, sinus rhythm; EDM, early diastolic murmur.
RVEDD: normal range 7 to 23 mm. Right ventricular endomyocardial fibrosis mean 47 mm, SD 11 mm.
LVEDD: normal range 35 to 56 mm. Left ventricular endomyocardial fibrosis mean 24 mm, SD 6 mm.
EDARVWT: normal <5 mm. Right ventricular endomyocardial fibrosis mean 9 mm, SD 2 mm.

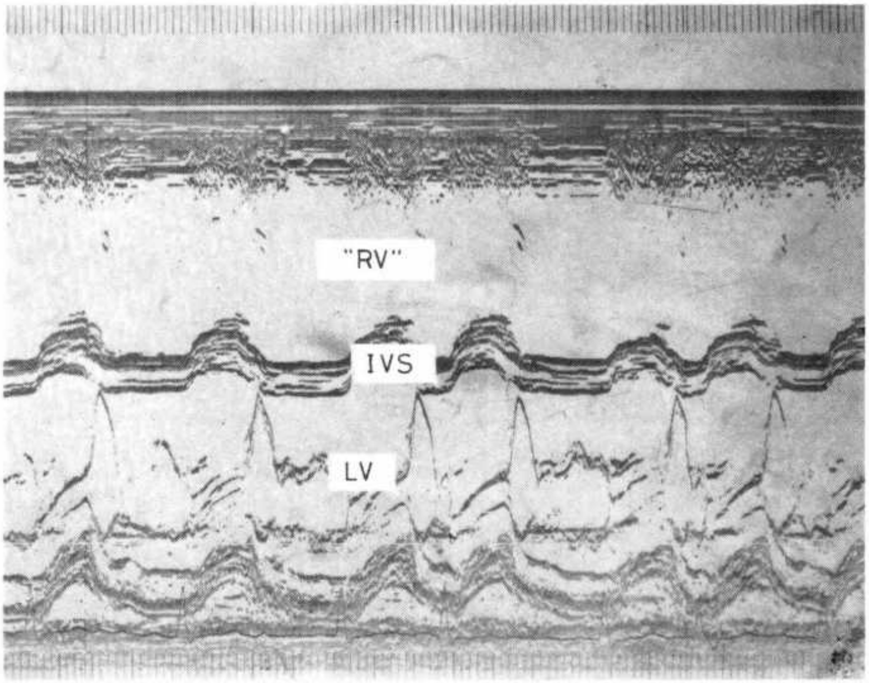

Fig. 1 *Echocardiogram in right ventricular endomyocardial fibrosis showing (i) increased right ventricular dimension, and (ii) paradoxical septal motion. RV, right ventricle; IVS, interventricular septum; LV, left ventricle.*

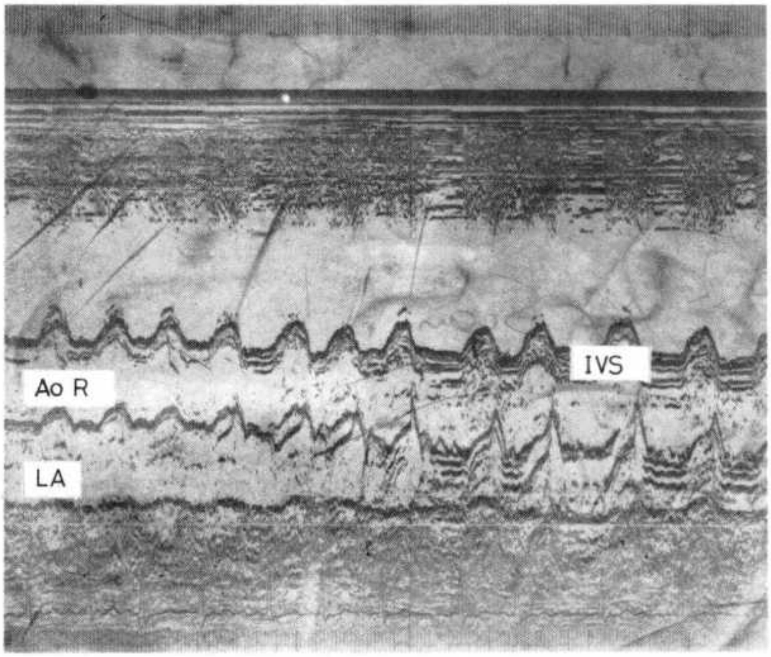

Fig. 2 *M-mode scan in right sided endomyocardial fibrosis showing increased dimension of the outflow tract. IVS, interventricular septum; Ao R, aortic root; LA, left atrium.*

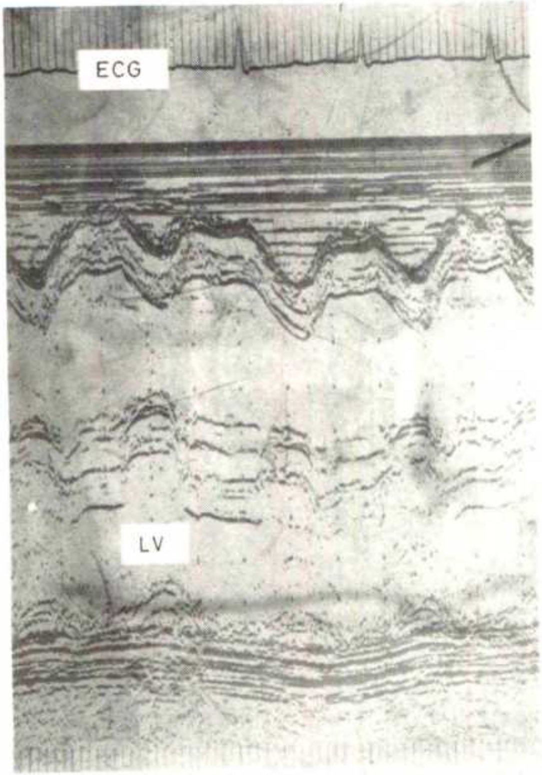

Fig. 3 *Echocardiogram in right ventricular endomyocardial fibrosis showing thickened and strongly contracting anterior right ventricular wall.*

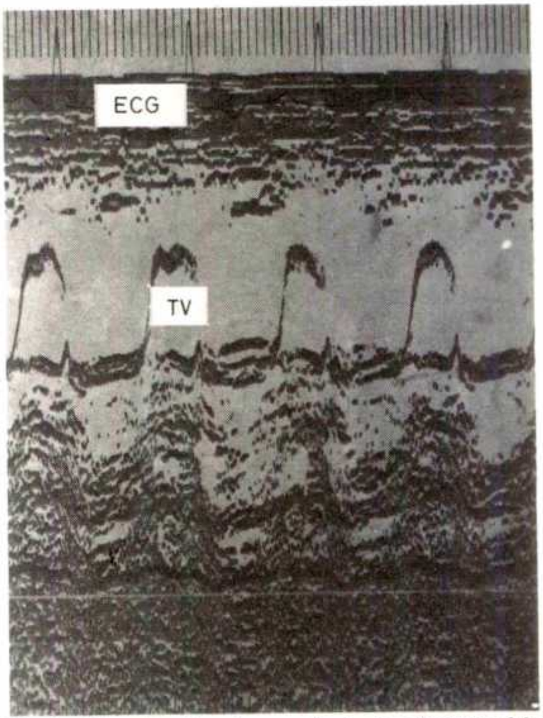

Fig. 4 *Tricuspid valve echogram showing fine fluttering of the anterior tricuspid valve leaflet. Electrocardiogram shows sinus rhythm.*

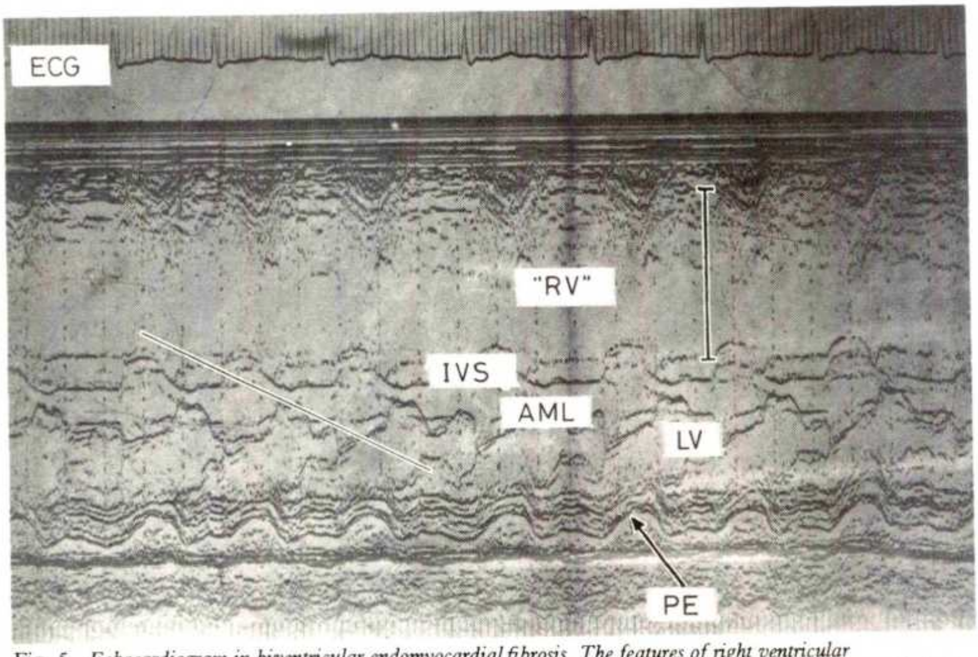

Fig. 5 *Echocardiogram in biventricular endomyocardial fibrosis. The features of right ventricular endomyocardial fibrosis are (i) dilated right ventricle (RV), (ii) pericardial effusion (PE), and (iii) paradoxical septal motion. The reduced left ventricular dimension of left sided involvement is shown.*

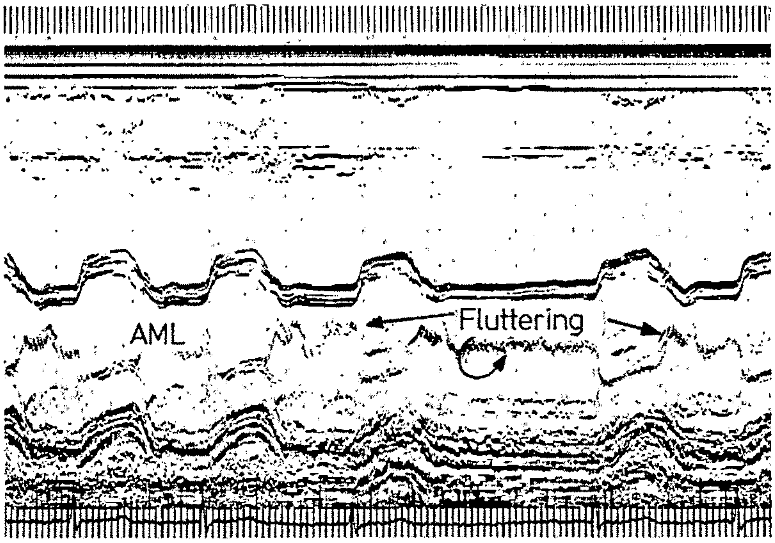

Fig. 6 *Fine fluttering of anterior mitral valve leaflet (AML). (See text.)*

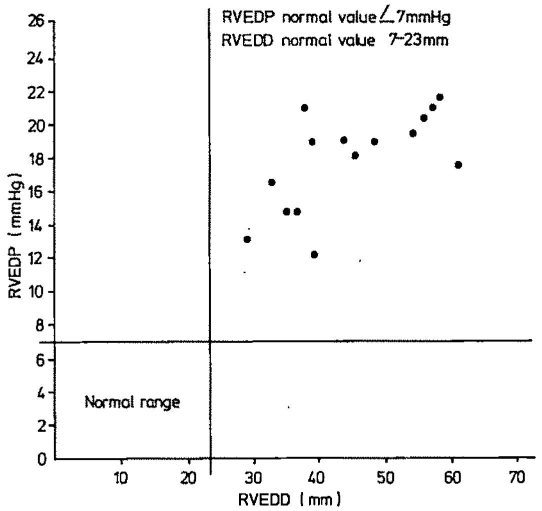

Fig. 7 *Right ventricular end-diastolic pressure (RVEDP) and echocardiographic right ventricular end-diastolic dimension (RVEDD) relation in 15 patients with right ventricular endomyocardial fibrosis. The end-diastolic pressure and echocardiographic dimension were raised in all 15. There was a significant degree of correlation between the RVEDP and RVEDD (r=0·683 p<0·005).*

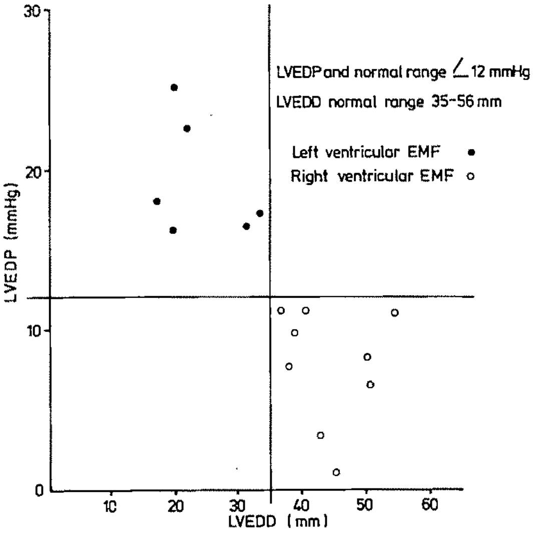

Fig. 8 *Left ventricular end-diastolic pressure (LVEDP) and echocardiographic left ventricular end-diastolic dimension (LVEDD) relation in 15 patients with endomyocardial fibrosis (nine with right ventricular and six with left ventricular involvement). The LVEDP was raised, and LVEDD reduced in patients with left ventricular endomyocardial fibrosis; the LVEDP and LVEDD were normal in right ventricular endomyocardial fibrosis. There was a highly significant correlation between LVEDD and LVEDP (r=0·82 p<0·005).*

wave (the patients were in sinus rhythm), and systolic notching of the pulmonary valve echocardiogram.

The echocardiograms in the two patients with constrictive pericarditis, and in two patients with gross ascites caused by portal hypertension were normal. One other patient showed echocardiographic features of tricuspid stenosis, namely, reduced e–f slope of the anterior tricuspid leaflet.

The 15 patients studied haemodynamically and angiographically showed the characteristic dip and plateau right ventricular pressure pattern with raised right atrial and right ventricular end-diastolic pressures. The six patients with left ventricular endomyocardial fibrosis had raised left ventricular end-diastolic pressures (Table). The right atrial angiograms showed a grossly dilated right atrial chamber with stasis of the contrast medium in the right atrium. The inflow tract of the right ventricle was obliterated and/or irregular, with distension of the outflow tract. The left ventricular angiogram showed changes consistent with left ventricular endomyocardial fibrosis in six patients (viz small, irregular chamber). There was also mitral regurgitation. Fig. 7 shows the relation of the right ventricular end-diastolic pressures to the echocardiographic right ventricular end-diastolic dimensions. Both were increased in all. The relation of the left ventricular end-diastolic pressures to the echocardiographic left ventricular end-diastolic dimension is shown in Fig. 8. The left ventricular end-diastolic pressures and left ventricular end-diastolic dimensions were normal in the nine patients with lone right ventricular endomyocardial fibrosis. The left ventricular end-diastolic pressures were raised and left ventricular end-diastolic dimensions diminished in patients with left ventricular involvement.

Discussion

Endomyocardial fibrosis, first described from Uganda in 1948 by Davies,[15] is characterised by fibrosis of the endocardium and the subendocardial layers of either the left or right ventricle, or both. The main feature[11 12] is deep scarring of the endocardium usually starting at the apex and spreading to the inflow tract, eventually affecting the papillary muscles, chordae, and posterior cusps of the atrioventricular valves, leading to mitral or tricuspid regurgitation. Macroscopically, the heart shows distortion and partial obliteration of the ventricles. There is normally moderate hypertrophy, and some hearts are greatly dilated, the dilatation mostly being the result of an enlarged right and/or left atrium. In right sided endomyocardial fibrosis, though there is apical obliteration and distortion of the cavity, the right ventricular outflow tract is dilated. There may be hydropericardium. Angiographic studies[9 10] have shown vigorous pulsation of the infundibulum of the right ventricle, tricuspid regurgitation, and a grossly dilated right atrium.

The echocardiographic features of increased right ventricular dimension and paradoxical septal motion in our patients with right sided endomyocardial fibrosis are not specific for endomyocardial fibrosis, and may in part result from the associated tricuspid regurgitation and/or pulmonary hypertension. This does not, however, explain these findings in those patients without tricuspid regurgitation or pulmonary hypertension. The paradoxical echocardiographic finding of increased right ventricular dimension in a disease that is characterised by cavity obliteration is difficult to explain. A possible explanation may be that, as a result of distortion of the heart and its axis, the ultrasound beam may be partly traversing the dilated right atrium as well as the right ventricle. The dilated right ventricular outflow tract and the vigorous anterior right ventricular wall contractions are in keeping with the pathological and angiographic findings in this disease, as is the reduced left ventricular dimension in left sided endomyocardial fibrosis. Apical obliteration of the cavity in right ventricular endomyocardial fibrosis, and strong echoes from the right ventricular endocardium have been reported by Hess *et al.*[10] and Hernandez-Pieretti,[13] respectively.

The aortic and pulmonary valves are not affected in endomyocardial fibrosis. Early diastolic murmurs have, however, been reported in a few cases of haemodynamically and angiographically proven endomyocardial fibrosis.[5 10] In the series reported by Davies and Ball,[16] in five cases the aortic valve had subacute bacterial endocarditis. In the two patients in our series with biventricular endomyocardial fibrosis in whom an early diastolic murmur was heard, aortic root angiograms were normal. Fine fluttering of the anterior mitral valve and tricuspid valve echogram was observed in these two patients.

Fine fluttering on an atrioventricular valve in the absence of aortic regurgitation, atrial fibrillation, or a high flow, is likely to be the result of distortion of the ventricular inflow tract and/or the valve apparatus by fibrosis. This mechanism may underlie the early diastolic murmur present in our two cases.

The echocardiographic features of left ventricular involvement are worth noting. These include a small left ventricular dimension, an increase in left atrial dimension, and the rather interesting inverse relation between the left ventricular end-diastolic pressure and end-diastolic dimension. The last is not seen in other types of left ventricular disease. Though the echocardiographic features found in our patients are not specific for endomyocardial fibrosis, they nevertheless are useful in resolving, non-invasively, any problems in diagnosis in these circumstances. Patients with constrictive pericarditis have similar clinical and haemodynamic features with right ventricular endomyocardial fibrosis. The echocardiographic features observed in our patients help to distinguish between right ventricular endomyocardial fibrosis and constrictive pericarditis.

Endomyocardial fibrosis was diagnosed in all clinically, and confirmed haemodynamically and angiographically in 15 and at necropsy in one. An attempt is made to correlate the echocardiographic findings with the haemodynamic findings, and to relate the echocardiographic findings to the angiographic findings. Though the echocardiographic features are not specific for endomyocardial fibrosis, they are characteristic, and useful in distinguishing non-invasively between endomyocardial fibrosis and other diseases which present with similar clinical features. In such circumstances, it is suggested that these echo features may be considered diagnostic of endomyocardial fibrosis, especially since these other conditions, for example rheumatic valvular disease and congestive cardiomyopathy, have characteristic echo features.

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Presentation White round biconvex tablets. 80 mg: scored on one side and engraved "Squibb" '241' containing nadolol 80 mg, 40 mg: engraved "Squibb" '207' containing nadolol 40 mg. **Indications** Corgard is indicated in the long-term management of angina pectoris and hypertension. **Dosage and administration** Dosage should be individually titrated. In elderly patients, particularly those with angina pectoris, a low initial dose should be used so that sensitivity to side effects may be assessed. Nadolol may be given in a once daily dosage without regard to meals. Angina Pectoris: Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily. The value and safety of daily doses exceeding 240 mg have not been established. Hypertension: Initially 80 mg once daily. This may be increased by a weekly increment of 80 mg or less until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have been required for a few patients. In some patients it is necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agent in conjunction with nadolol in order to achieve satisfactory response. Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent. **Contra-indications** Bronchial asthma, sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure. **Warnings** The normal precautions associated with the use of beta-adrenergic blockers should be followed. Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency. When discontinuing long-term nadolol therapy the dosage should be reduced gradually over a period of at least two weeks. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus. Care should be taken in administering nadolol during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors. The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential. **Side-effects** These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. Those reported infrequently include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insuffiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically. **Legal category** Prescription only. **Product Licence Numbers** 80 mg – 0034/0186 40 mg – 0034/0185. **Package Quantities** Bottles of 100 tablets. Cost per 80 mg tablet, 16p. Cost per 40 mg tablet, 11p. ▼ Special reporting to CSM required. Corgard is a Trade Mark of E.R. Squibb & Sons Ltd.

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1. Lancet 1980; 1: 693 2. Br J clin Pharm 1979; 7: (Suppl 2) 219S
3. In: Gross F, ed. International Experience with Nadolol – a long-acting β-blocking agent: symposium, Paris, December 5–7, 1980 London: R Soc Med No 37 1981 25–30

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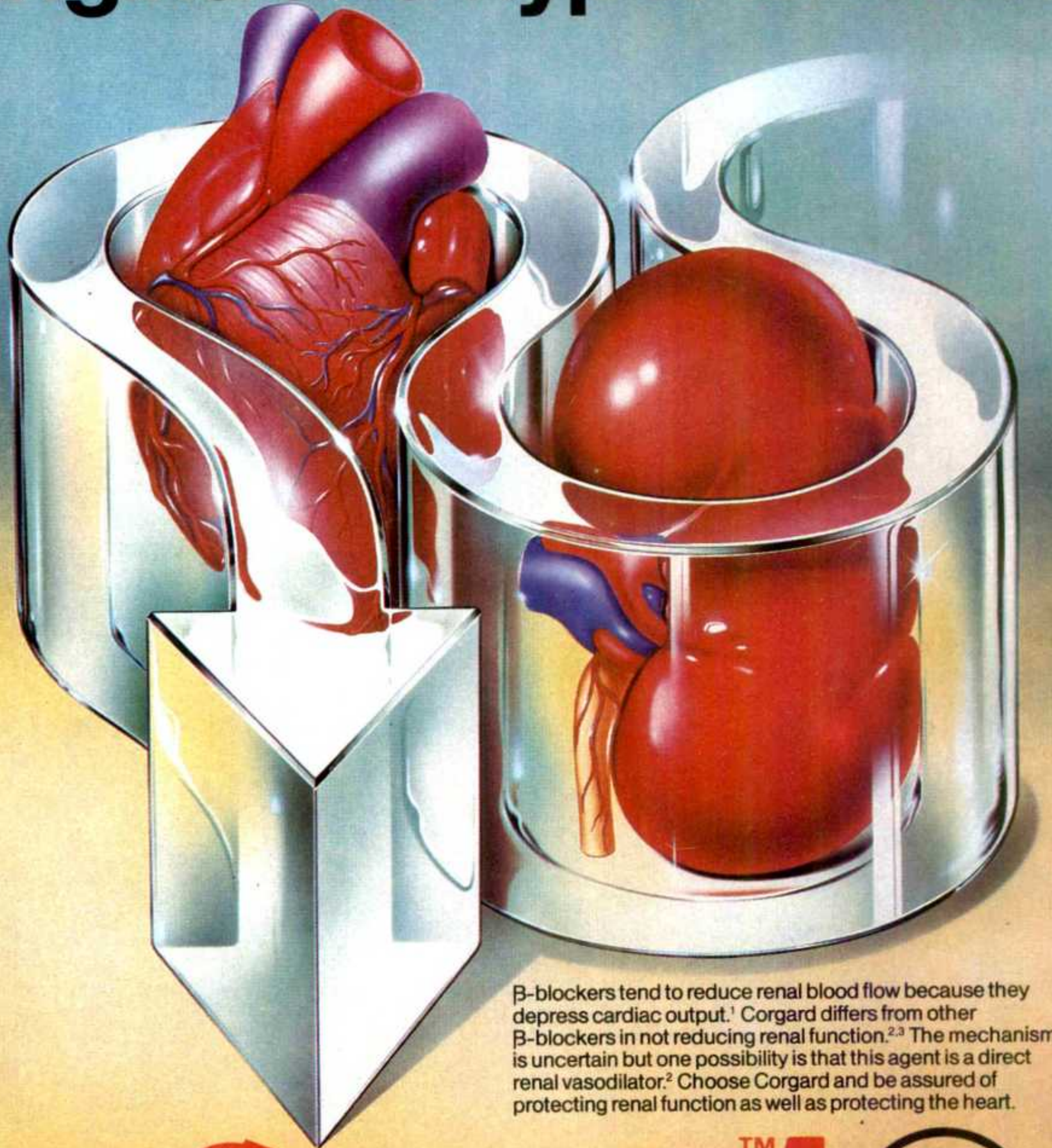

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Br Heart J 1982; **48**: 229–35

Cross-sectional echocardiographic recognition of interruption of aortic arch between left carotid and subclavian arteries

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SUMMARY Interrupted aortic arch is a rare condition, usually lethal in early infancy without treatment. The only characteristic feature on conventional non-invasive investigation is peripheral pulse inequality, which indicates ductal constriction, and therefore may be absent or transient and preterminal.

We report the cross-sectional echocardiographic findings in seven patients with aortic arch interruption between the left carotid and subclavian arteries. Their ages were 1 day to 7 months (median 7·5 days). The arterial connection was concordant in four, double outlet right ventricle in two, and truncus arteriosus in one.

In each case the ascending aorta was small in comparison to the pulmonary trunk. From the suprasternal approach the ascending aorta could be seen to terminate in the left carotid artery, and the ductus to continue smoothly into the descending aorta, with no vestige of an aortic arch linking its ascending and descending portions. The left subclavian artery was seen to arise distal to the ductus in all but one patient. All four patients with ventriculoarterial concordance had pronounced subaortic stenosis caused by posterior displacement of the infundibular septum.

Cross-sectional echocardiography therefore provides the only accurate method of non-invasive diagnosis of this condition. It permits early treatment with prostaglandins to prevent ductal closure, a planned approach to cardiac catheterisation, and a further means of investigating the nature of subaortic stenosis in this condition.

Interruption of the aortic arch is a rare congenital anomaly, usually lethal in infancy, because of complete dependence of part of the systemic circulation on patency of the ductus arteriosus.[1 2] Standard physical examination, chest radiography, electrocardiography, and M-mode echocardiography usually do not provide the means of specific recognition of the condition. Yet neonates with aortic arch interruption urgently need administration of prostaglandins to maintain duct patency,[3–5] preferably before cardiac catheterisation is initiated.

Recent advances in imaging of the aortic arch by cross-sectional echocardiographic examination from the suprasternal notch[6] led us to believe that aortic arch interruption should be diagnosable by this method. We therefore report the findings in seven patients with aortic arch interruption studied at this hospital over the past 14 months.

Subjects and methods

Between November 1980 and February 1982, seven infants were admitted to The Hospital for Sick Children who turned out to have aortic arch interruption, in each case between the left carotid and subclavian arteries. In three of these (Table), angiocardiography in another hospital had shown the diagnosis of aortic arch interruption, but in the remaining four, the diagnosis of aortic arch interruption was prospectively and correctly made by cross-sectional echocardiography. A combination of subcostal, precordial, and suprasternal approaches was used in each patient. Atrial situs was established from high kilovoltage filtered beam radiographs of the bronchi, and from echocardiography by short axis views of the abdomen to show

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Table *Summary of findings in seven patients with interrupted aortic arch*

Case No.	*Age*	*Sex*	*AV connection**	*VA connection*	*VSD*	*Infundibular septal displacement*	*Angio preceded echo*	*Confirmation† of intracardiac anatomy*	*Confirmation† of extracardiac anatomy*
1	5 mth	M	Concordant	Concordant	Perimembranous outlet	Posterior	+	Necropsy	Necropsy
2	2 d	M	Concordant	Concordant	Muscular outlet	Posterior malaligned	–	Angio	Surgery
3	1 d	F	Concordant	Concordant	Muscular outlet	Posterior malaligned	–	Angio	Surgery
4	7 d	F	Concordant	Concordant	Perimembranous trabecular	Posterior	–	Necropsy	Necropsy
5	2 mth	F	Concordant	DORV	Inlet muscular and doubly committed subarterial (subaortic)	Absent	–	Angio	Angio
6	8 d	M	Concordant	DORV	Perimembranous outlet (subpulmonary)	Anterior	+	Angio	Surgery
7	7 mth	F	Concordant	Truncus	Outlet subarterial	Absent	+	Necropsy	Necropsy

*All patients had situs solitus; †Most certain level given.

Angio, angiocardiogram; AV, atrioventricular; d, days; DORV, double outlet right ventricle; echo, echocardiogram; mth, months; VA, ventriculoarterial; VSD, ventricular septal defect.

the relation of the aorta and inferior vena cava to the spine. In addition, pulmonary venous and systemic venous connections were noted. The atrioventricular connection was established from subcostal four-chamber views of the atrioventricular junction, together with identification of ventricular morphology from the appearance of the atrioventricular valves and their chordal insertions. The ventriculoarterial connection was determined from study of the ventriculoarterial junction in subcostal long axis, precordial long and short axis, and suprasternal cuts.

Particular attention was paid to suprasternal notch examination. The transducer was initially placed in the suprasternal notch with its beam in the frontal plane of the body. In this cut, the right pulmonary artery was imaged in its long axis, lying above the left atrium, with the aorta appearing in its short axis. Next the transducer was rotated anticlockwise in an attempt to trace the aorta in its long axis. In this position the origin of the brachiocephalic and left subclavian arteries was sought. Particular care was taken to try and visualise that part of the aortic arch between the left carotid and left subclavian arteries together with the isthmus. Next the transducer was rotated clockwise until the aorta was visualised in its short axis. The scan head was then angled towards the right shoulder following the origin of the brachiocephalic artery into its carotid and subclavian branches. In this procedure care must be taken to trace the artery to the aorta, so that confusion with venous bifurcations does not occur. The transducer was then rotated anticlockwise, with angulation towards the patient's left shoulder. Initially the pulmonary trunk was visualised and then, as the scan head was angled further, the left pulmonary artery was seen. The persistent ductus arteriosus was imaged lying directly above the left pulmonary artery. Great care was taken to visualise both aortic and pulmonary ends of the patent ductus.

The patients were studied with an Advanced Technology Laboratory mechanical sector scanner with a 5 MHz scan head. Images were recorded on ½ or ¾ inch video tape and analysed frame by frame using a Sony Motion Analyser. Images were obtained from stop frames on the analyser using standard Tri-X film (ASA 400). Correlation with necropsy findings was illustrated by use of specimens from the collections of The Hospital for Sick Children, Great Ormond Street, the Cardiothoracic Institute, the Brompton Hospital, and the Institute of Child Health, University of Liverpool.

Results

These are summarised in the Table. All patients had situs solitus and atrioventricular concordance. The ventriculoarterial connection was concordant in the first four patients, and double outlet right ventricle in two. Case 7 had truncus arteriosus, with separate origin of the right and left pulmonary arteries from the truncus arteriosus. All of the abnormalities of connection were easily recognisable on cross-sectional echocardiography.

AORTIC ARCH INTERRUPTION

The first clue to the presence of interruption of the aortic arch in all patients was the discrepancy between the size of the ascending aorta and pulmonary trunk (compare Fig. 1 and Fig. 2). In most cases, the diameter of the ascending aorta was at the lower limit of normal[7] whereas the pulmonary trunk was huge. The size of the pulmonary trunk was such that it was possible in most patients to obtain a cut extending from the pulmonary valve or just above all the way along the pulmonary trunk and through the ductus

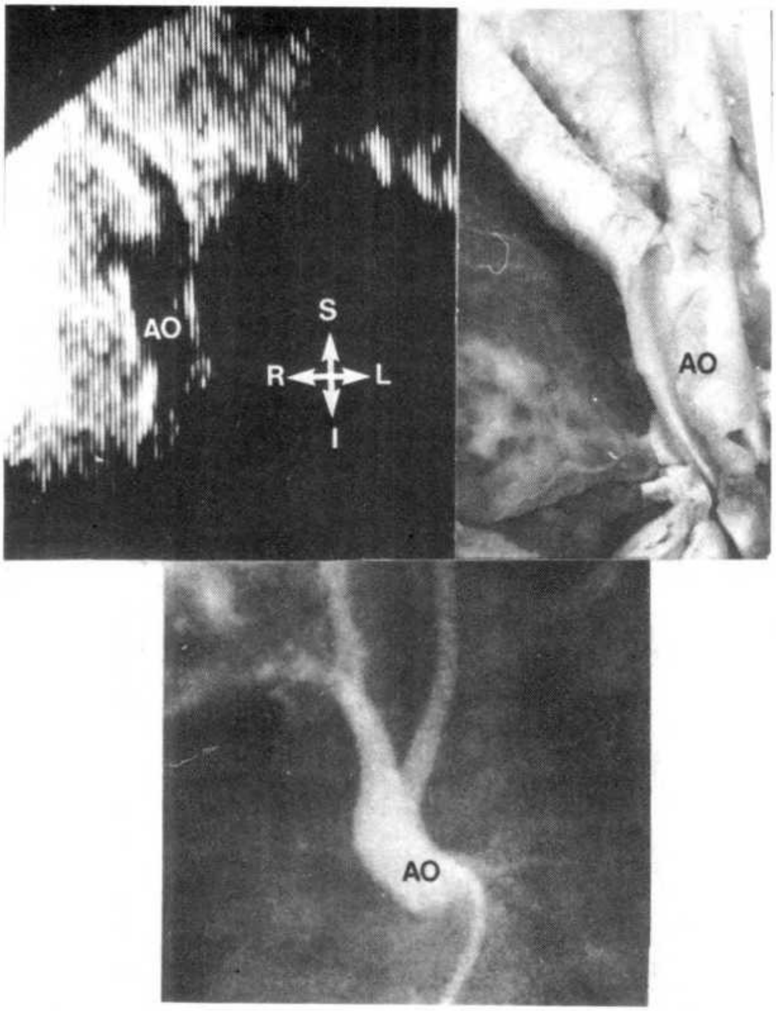

Fig. 1 *The upper left picture is an echocardiogram from a case with an interrupted aortic arch distal to the left carotid. Note the origin of the brachiocephalic artery is also seen. The angiocardiogram is from the same patient. The necropsy specimen from a different case illustrates the anatomical features. AO, aorta.*

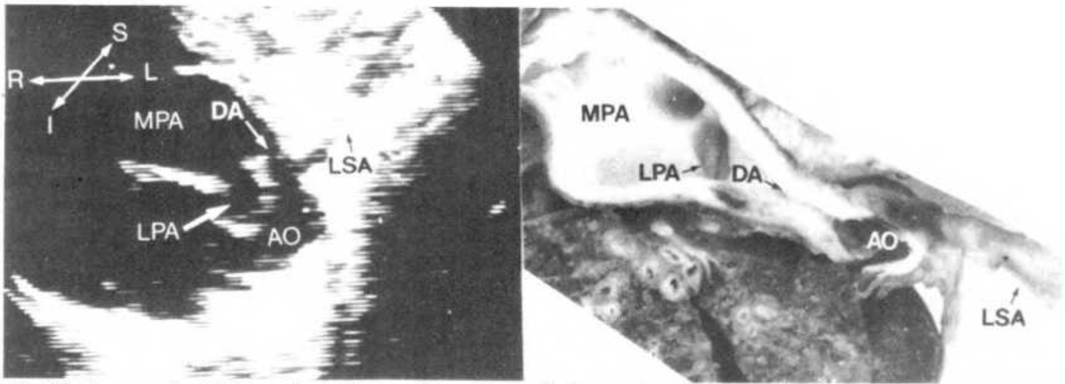

Fig. 2 *The image on the left is an echocardiogram from a case with interruption showing the ductus arteriosus connecting the main pulmonary artery and descending aorta. Note the left subclavian artery arises from the descending aorta. In this cut there is no upper descending aorta visible. The specimen on the right is from a different case illustrating the morphological features. DA, ductus arteriosus; LPA, left pulmonary artery; LSA, left subclavian artery; MPA, main pulmonary artery; AO, aorta.*

arteriosus into the descending aorta (Figs. 2 and 3). This appearance might at first sight have been confused with that of a transposed aorta continuing into a normal aortic arch except that the left pulmonary artery (and in six patients the right pulmonary artery also (Fig. 3)) could be seen originating from the pulmonary trunk in this cut. The left subclavian artery was clearly identified apparently arising from the descending aorta (Fig. 2) in all but case 3. The ductus arteriosus was a wide open structure with walls as smooth as the pulmonary trunk and descending aorta (Fig. 4) in the three patients aged 2 months old and above. In the remaining four patients, there was a greater or lesser degree of ductal constriction, manifested as intimal cushions projecting into the lumen (Fig. 3). Whether the ductus was wide open or constricted, however, the superior margin of the pulmonary trunk continued cleanly into the posterior margin of the descending aorta (Fig. 4).

The ascending aorta could be traced back to the aortic valve in all patients except the one with a truncus arteriosus, in whom the small ascending aorta was followed back to a huge common arterial trunk (Fig. 4) originating above a quadricuspid truncal valve. In all patients the origin of the brachiocephalic artery from the ascending aorta was identifiable (Fig. 1), though it was traced to its bifurcation (Fig. 5) in only four. In every patient, the left carotid artery gave the appearance of an index finger pointing towards the neck, with the carotid artery continuing smoothly on from the ascending aorta, with no suggestion of an aortic arch being present at all. Indeed, it was only possible in cases 3 and 4 to image the

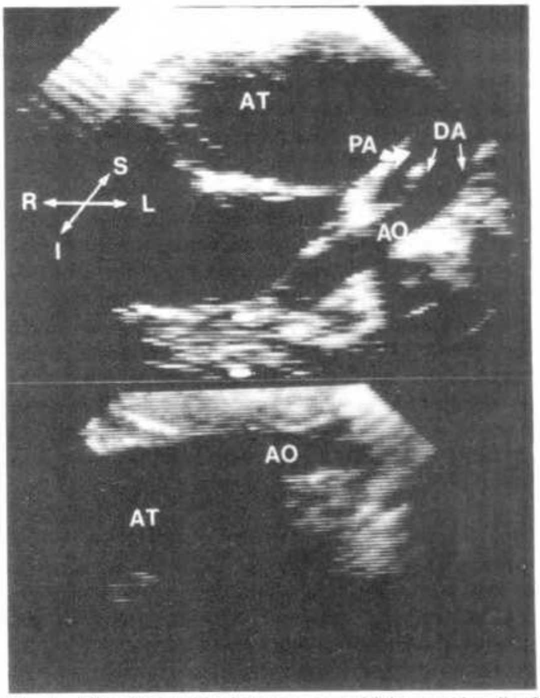

Fig. 4 *The upper picture is from a case with interruption distal to the left carotid, associated with truncus arteriosus. Note the large ascending trunk and the ductus arteriosus connecting it to the descending aorta. The origin of the pulmonary artery is also seen. The lower picture is from the same case and shows the ascending aorta to its site of interruption. AT, ascending trunk; PA, pulmonary artery (for remaining abbreviations see Fig. 1 and 2).*

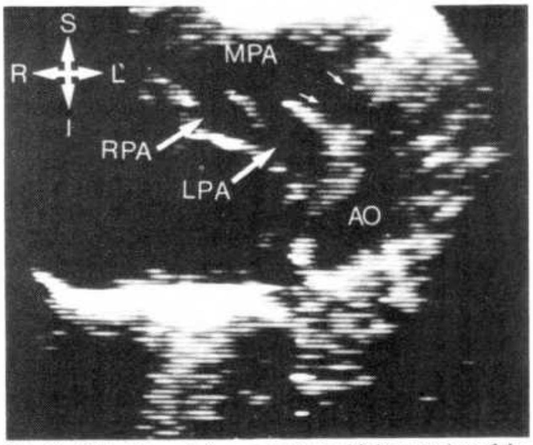

Fig. 3 *This picture is from a patient with interruption of the aortic arch. The cut which is suprasternal shows the main, left, and right pulmonary arteries and the ductus in the same plane. Note the lumen of the ductus is irregular (arrows). RPA, right pulmonary artery (for other abbreviations see Fig. 1 and 2).*

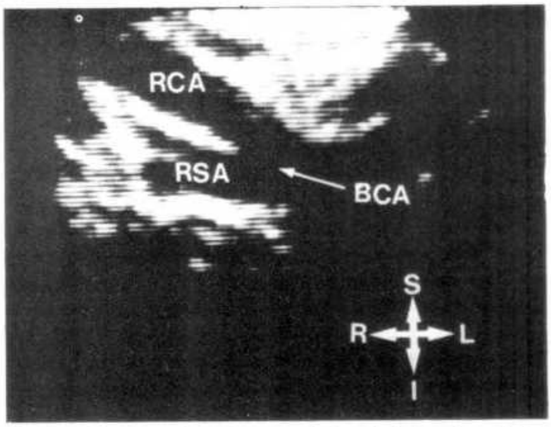

Fig. 5 *The picture is a suprasternal view of the brachiocephalic artery in a case with interruption. Note the artery points to the right side (showing a left arch) and divides into the right carotid and subclavian branches. BCA, brachiocephalic artery; RCA, right carotid artery; RSA, right subclavian artery.*

ascending and descending aorta in the same plane (Fig. 6). The two were discontinuous and it was clear that the ascending aorta continued into the left carotid artery without attempting in any way to form a transverse segment of aortic arch.

SUBSTRATES FOR SUBAORTIC OBSTRUCTION

The relative smallness of the ascending aorta already mentioned extended to the aortic valve and subaortic region in all patients except the one with truncus arteriosus. In those patients with ventriculoarterial concordance, the long axis cut of the left ventricle showed posterior displacement of the infundibular septum of a pronounced degree in each case. In cases 2 and 3, in whom a ventricular septal defect of muscular outlet type appeared small in the long axis cut, malalignment between the trabecular and infundibular septa was obvious. The superior portion of the infundibular septum lay in line with the trabecular septum, but as the infundibular septum was followed inferiorly, it curved posterior to the trabecular septum (Fig. 7). This malalignment was not so obvious in cases 1 and 4, where the ventricular septal defect was much larger and involved the perimembranous region. In each case, however, the posterior displacement of the infundibular septum gave the appearance of severe subvalvular aortic stenosis. Interestingly, in the first patient there was only a 5 mmHg systolic gradient between left ventricle and ascending aorta, and in cases 2, 3, and 4 there was no gradient at all between these sites. The subaortic region appeared crowded in case 6, who had double outlet right ventricle with a subpulmonary ventricular septal defect, but no pressure was available in the ascending aorta. Thus, the only two patients in whom there was no echocardiographic suggestion of subaortic obstruction were the patient with a truncus, and the patient with double outlet right ventricle with a large subaortic ventricular septal defect extending to the junction between the aortic and pulmonary valves.

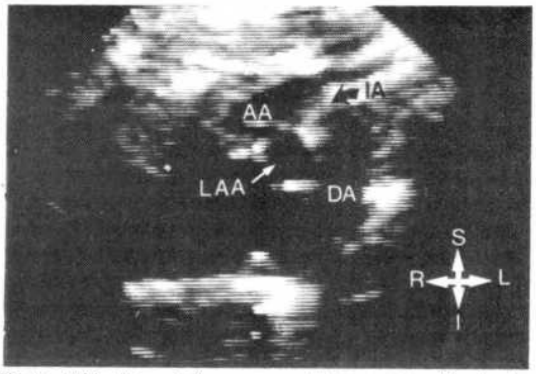

Fig. 6 *This picture is from a case with interruption distal to the left carotid. Note the site of interruption is clearly seen, but in this patient the upper descending aorta can be visualised in the same cut, and is of a reasonable calibre. AA, ascending aorta; DA, descending aorta; IA, interrupted aorta; LAA, left atrial appendage.*

The only patient with an atrial septal defect was case 6, who had had a balloon atrial septostomy elsewhere. Pronounced bulging of the atrial septum from left to right was seen in cases 3 and 5. In the remainder the position of the atrial septum was more or less normal.

Discussion

Interruption of the aortic arch is a rare condition, occurring in 19 per million live births in the New

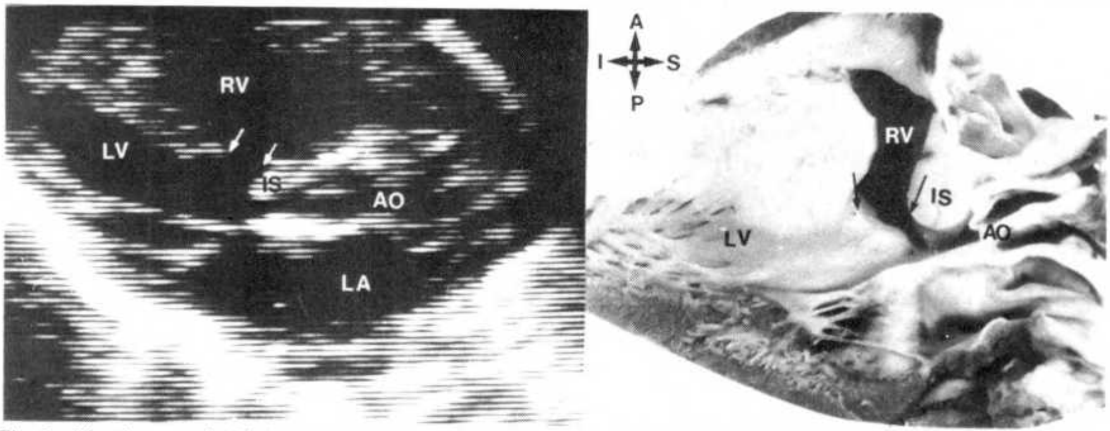

Fig. 7 *The picture on the left is a parasternal long axis cut from a case with interruption. Note the posterior displacement of the infundibular septum into the left ventricular outflow tract. The ventricular septal defect (indicated by the arrows) is muscular, and situated in the infundibular septum. The specimen on the right is cut in the same plane and shows the echocardiographic features, though it is from a different patient. AO, aorta; IS, infundibular septum; LA, left atrium; LV, left ventricle; RV, right ventricle.*

England regional infant cardiac program.[8] The sex incidence is equal.[1] About 10% of patients have DiGeorge syndrome (thymic aplasia), and about 40% have serious associated non-cardiac congenital abnormalities.[9] Nearly all patients present as neonates in severe intractable heart failure: 80% are admitted to a specialist hospital within 2 weeks and 93% by 1 month.[10] In necropsy series from children's hospitals, the median age at death was 4[2] and 10[1] days, respectively. Though this is bound to present a somewhat pessimistic view of the natural history, it does underline the exceedingly poor prognosis of this condition.

Interruption occurs very occasionally between the two carotid arteries. In the remaining cases interruption between the left carotid and subclavian arteries is slightly commoner than interruption distal to the left subclavian artery at the isthmus.[1] By sheer chance, all the patients in this series had interruption distal to the left carotid artery.

Very occasionally, interrupted arch occurs as an isolated phenomenon, in which case descending aortic blood flow is maintained from systemic collateral circulation.[11] In the vast majority of cases, however, particularly those presenting in the neonatal period, blood flow to the descending aorta is provided by a right to left shunt through the ductus arteriosus. This in turn depends upon there being pulmonary hypertension, and a pulmonary vascular resistance sufficiently high to ensure right to left shunting through the ductus arteriosus. In the majority of cases, pulmonary hypertension is maintained by the coexistence of a large ventricular septal defect without pulmonary stenosis. Much more rarely, an aortopulmonary window serves the same purpose.[12] A left to right shunt through the ventricular septal defect tends to bring the saturations in the aorta and pulmonary artery close together, so that differential cyanosis on either side of the aortic arch interruption is extremely rare.[13] Furthermore, while the ductus remains widely patent, the pulses distal to the interruption are well maintained. Indeed, pulse inequality has been mentioned as a distinctive physical sign[10 14] only in more recent descriptions of aortic arch interruption. This is presumably because the sign is often only transitorily present. Such pulse inequality may take various forms, according to the site of interruption and the origin of the subclavian arteries. Ductal constriction invariably reduces the femoral pulses. If both subclavian arteries originate distal to the interruption, ductal constriction will in addition reduce the arm pulses, leaving only the carotid and superficial temporal pulses spared. More commonly, the left arm pulse is reduced by comparison with that in the right arm, indicating interruption distal to the left carotid with normal origin of the right subclavian artery. In theory, interruption between the brachiocephalic and left carotid artery should result in inequality between the two carotid or superficial temporal arteries. Whatever the precise nature of the pulse inequality, it reflects ductal constriction. If the patient survives, it is because the ductus has reopened, and the pulse inequality will have disappeared. If the ductus goes on to close, the patient will become moribund and no pulses will be palpable. Hence, unless this transitory physical sign is detected, there is no specific clue in the standard investigation of the patient, including M-mode echocardiography, to suggest the presence of interruption of the aortic arch. Yet the rapidity of normal neonatal ductal closure means that it is highly desirable to be able to make the diagnosis of aortic interruption before pulse inequality is found.

This study clearly shows that correct non-invasive diagnosis is possible with cross-sectional echocardiography. The appearance of the ascending and descending aorta in no way resembles a normal aortic arch, even one affected by coarctation or isthmal hypoplasia. The "pointing finger" appearance of the left carotid artery corresponds to the characteristic "V-sign" on angiocardiography.[15] Both are the result of the ascending aorta continuing into the carotid artery instead of into the aortic arch. The reason that the "V-sign" is not so well seen on cross-sectional echocardiography is that the carotid and brachiocephalic arteries lie in different planes, such that it is not possible to image the ascending aorta in continuity with the carotid artery, and in the same plane see anything more than the beginning of the brachiocephalic artery (Fig. 1). Failure to demonstrate the ascending and descending aorta in the same cut, as occurred in all but two of our patients, may be surgically relevant, since it suggests a wide gap between the two.

It is important to trace all the branches of the aorta, if at all possible, because it is not sufficient to guess the origin of an artery which is not seen. This is particularly true of the subclavian arteries, which may be isolated, that is arising via a second ductus from the pulmonary artery[1 16] or else much more frequently, in the case of the right subclavian, may originate anomalously from the descending aorta. We were not successful in every case in identifying both subclavians, but believe this reflects lack of practice more than an insoluble technical problem. We also know in the cases studied that the right subclavian arose directly from the brachiocephalic artery. The left subclavian artery, when identified, gave the appearance of originating from the descending aorta. In *sensu strictu* there is, of course, a segment of isthmus (transverse arch) between descending aorta and subclavian, and this may be the substrate for the stenosis noted at the origin of the left subclavian in this type of interruption by Dische and colleagues.[11] Such a stenosis was not observed in these patients.

Once the diagnosis is established by cross-sectional echocardiography, in the neonate, prostaglandin infusion should be started[3–5] whether or not there is any evidence of ductal closure or constriction. This means that the patient can go to the cardiac catheterisation laboratory in the best possible condition, and that the invasive study can be carried out with emphasis on any features which have not been clearly shown by cross-sectional echocardiography. In this particular condition, we do not recommend surgery without cardiac catheterisation and angiocardiography, because there are still too many unanswered questions about what management is optimal.

The most striking of these problems is the role of subaortic stenosis. While the presence of subaortic stenosis caused by posterior displacement and rotation of the infundibular septum has clearly been described at necropsy,[1 2 17] by angiocardiography,[15] and now by cross-sectional echocardiography, in the majority of cases the anatomical abnormality has not been associated with a pressure gradient between the ventricles and the ascending aorta. This may in part be the result of a hitherto unmeasurable, but probably low, flow through the aortic valve. Though closure of the ventricular septal defect in such cases should not of itself increase the degree of left ventricular outflow tract obstruction, since the ventricular septal defect is upstream to the infundibular septum, postoperatively, the left ventricle will have to eject its entire stroke volume through the subaortic region, instead of shunting most of this left to right through the ventricular septal defect. It was Tyson and colleagues[18] who originally suggested that in those patients with subaortic stenosis, the preferred operation was anastomosis of the pulmonary trunk to the descending aorta, with banding of the pulmonary arteries distal to the anastomosis, rather than any repair involving restoration of aortic continuity. Unfortunately, we do not know what the degree of subaortic obstruction was in those patients who have survived or not survived definitive surgery. It seems very likely, however, that some of the high mortality of surgery for this condition is the result of unrelieved subaortic stenosis. Cross-sectional echocardiography therefore provides not only a highly accurate means of making the diagnosis of aortic arch interruption, but also a further means of examining the subaortic region, which should, in the long run, help with optimal surgical management of this condition.

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Complete congenital heart block
Report of 35 cases

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SUMMARY Congenital complete atrioventricular block is uncommon, and the outlook is usually regarded as favourable. Thirty-five patients with congenital heart block are presented. There was no obvious sex difference and their ages ranged from 12 days to 85 years, though most were under the age of 20 years when first seen. Accompanying heart disease was noted in six, but presentation with symptoms in early infancy was a more serious risk factor in our experience. Permanent pacing was required in 21, three of whom were neonates. One of the 14 unpaced patients died unexpectedly at the age of 5 years. Long term supervision is necessary, as most will require permanent pacing before their 50th birthday.

Acquired third degree atrioventricular heart block in adults is relatively common, being attributed most frequently to degeneration of the fibres in the conducting system.[1] Congenital complete heart block, by contrast, is rare. It was first described by Morquio,[2] who reported a family in which several sibs had pronounced bradycardia and syncopal attacks, with death in early childhood. We encountered 35 patients with congenital heart block, and the purpose of our paper is to try and assess the incidence of the condition in our region, the possible prognosis, and from the study to define the indications for establishing permanent pacing.

Patients and methods

Over a period of 18 years (1962 to the end of 1980) we encountered in our region in south-west Scotland a total of 35 patients with congenital complete atrioventricular block. All fulfilled the criteria defined by Yater[3]: a slow heart known to have been present from birth or from a very early age; the absence of a history of diphtheria or other myocarditis which might cause heart block; no evidence of ischaemic heart disease or cardiomyopathy; no previous cardiac surgery.

Fifteen of the patients were male and 20 female. The age at presentation is tabulated (Table 1). The youngest patient was 12 days old and the oldest was a man of 85 years known to have had a slow heart rate since early childhood and who was subsequently discharged from military service in the first world war on this account. He remained symptom free until his mid-eighties when he developed syncopal attacks and was referred for permanent pacing.

Of the four who presented in early infancy, three had symptoms and required early, permanent pacing, while the fourth who had no symptoms was discovered to have bradycardia on routine medical examination. The remaining patients were referred in later childhood or early adult life because of the finding of a slow heart rate, with or without symptoms. Long term supervision was considered mandatory in all. Twenty-one patients required the insertion of a permanent pacemaker and they are considered separately from, and compared with, the 14 who were not paced.

ACCOMPANYING CARDIAC DEFECTS

Six of our patients (17%) had accompanying congenital cardiac defects. These comprised three with ventricular septal defect, two with persistent ductus arteriosus, and one with coarctation of the aorta with

Table 1 *Age in years at presentation of 35 patients with congenital heart block*

0–11/12	*1–4*	*5–9*	*10–19*	*20–29*	*>30*
4	2	8	13	5	3

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persistent ductus arteriosus. In the remaining 29 congenital heart block was the sole anomaly.

Results

PERMANENT PACING

Permanent pacemakers were inserted into 21 patients because of symptoms comprising either syncopal attacks or signs of early cardiac failure. Only one had an accompanying cardiac defect, an infant of 3 weeks old in cardiac failure with coarctation of aorta. This was repaired surgically and a pacemaker implanted as an emergency procedure. The age at which pacing was established is set out in Table 2.

The three youngest patients were aged 12, 21, and 22 days. Emergency pacing was required because of frequent syncopal attacks in two and of advanced cardiac failure in one. At thoracotomy the pacing leads were anchored to the external surface of the heart and attached to a generator embedded either in the costophrenic sulcus or subcutaneously in the anterior abdominal wall. A small mercury chloride Medtronic pacemaker with a rate set at 120 a minute was used and replaced at two years and again at five years by a larger lithium generator.

There were no deaths or complications in the pacemaker group. All have been followed up and have remained well one to 12 years since the start of pacing.

PATIENTS NOT PACED

Fourteen patients did not undergo permanent pacing. One of these, a 5 year old boy, died quite suddenly and unexpectedly at home after a short illness accompanied by diarrhoea and vomiting. He had been free from symptoms and had no obvious accompanying cardiac defect. The electrocardiogram had shown complete heart block, with a resting heart rate of 47 and a normal QRS and QT interval. No obvious cause of death was found at necropsy.

Only one patient developed symptoms, a girl who at the age of 18 years experienced several mild syncopal attacks. In view of the unreliability of pacemakers at the time (1963), treatment with sustained release isoprenaline was started as an alternative. The attacks became less troublesome and eventually disappeared. Subsequently she had three uneventful pregnancies, and now at the age of 36 years is well with only mild dyspnoea. The resting heart remained unaltered at 44 a minute.

Table 2 *Age in years at pacemaker implantation in 21 patients with congenital heart block*

0–11/12	*1–4*	*5–9*	*10–19*	*20–29*	*30–49*	*>50*
3	0	0	5	2	9	2

Table 3 *Present age in years of 13 unpaced patients with congenital heart block*

0–11/12	*1–4*	*5–9*	*10–19*	*20–29*	*30–39*
1	1	2	3	5	1

The remaining 12 in this group were referred in late infancy, later childhood, or adult life because a slow heart rate had been found on routine examination. All remained well. The current age of the surviving nonpaced patients is as shown (Table 3).

ANALYSIS OF ELECTROCARDIOGRAM AND HEART RATE

The electrocardiograms of all the patients were closely studied to find out whether there were any differences between those who required pacing and those who did not. The heart rate varied from 38 to 60, but in no patient did the QRS complex exceed 0·12 second. The QT interval measured 0·48 in one patient only, an infant of 21 days who required emergency pacing. In the remaining 34 the QT interval was less than 0·43 second.

ATTEMPT AT ASSESSING PROGNOSIS IN CONGENITAL HEART BLOCK

Emergency pacing was necessary in three out of four who presented in early infancy (Tables 1 and 2). The remaining 31 were first seen after the age of 1 year and none required a pacemaker until the second decade of life. Of these 31, 18 eventually required pacemakers, most of them between 10 and 49 years. Only two patients survived beyond their 50th birthday without the need for permanent pacing.

Discussion

In the absence of any reliable figures, it is difficult to define precisely the incidence of congenital complete heart block in the community. It is relatively uncommon compared with the incidence of acquired heart block in adults. Keith and his associates at Toronto Children's Hospital[4] found 90 cases of congenital heart block out of 15 104 patients with congenital heart disease between 1950 and 1973. In an international study from 44 paediatric centres in Europe, the United States, Canada, and Mexico[5] a total of 599 infants and children with congenital heart block was collected. It was estimated from this study that the incidence lay between one in 15 000 and one in 20 000 live births. The annual birth rate for south-west Scotland (population approximately three million) for the last few years has been 40 000 which would produce two cases of congenital heart block each year. In 18 years (the period under review in our study) the figure would be 36, which corresponds very closely with the total number we encountered.

Several histological studies have been reported in congenital heart block in an attempt to localise the site of block and its cause.[6-8] In a further study on postmortem specimens the presence of aberrant fibrous tissue either at the level of the atrioventricular node or the atrioventricular bundle was demonstrated histologically.[9] The conclusion was that this tissue interrupted normal conduction pathways, producing discontinuity between the atria and atrioventricular node or between the node and ventricular conducting tissues. His bundle studies may help to localise the site of the block.[10 11] In congenital heart block with no accompanying cardiac lesion this is situated most frequently proximal to the bundle of His.[12] We did not carry out any His bundle recordings in any of our patients.

Recently several observers reported an association between congenital heart block in newborn infants with maternal connective tissue disease, particularly systemic lupus erythematosus.[13-16] We were unable to trace any such relation in any of our patients on clinical grounds, though laboratory evidence was not available in all of them.

The prognosis in congenital heart disease particularly when there is no accompanying heart defect appears to be favourable according to reports.[4 5] It can be compatible with normal growth and development,[17] and some patients have survived to their 40's or even 60's without pacing.[18 19] In rare isolated cases, return to sinus rhythm has occurred spontaneously,[20 21] though this is more likely in heart block complicating surgical repair of congenital cardiac defects.[22-24] Successful pregnancy in patients with congenital heart block, who have not been paced, has been reported.[25] One of our unpaced patients had three uneventful pregnancies despite previous syncopal attacks.

Such a favourable prognosis is not uniform throughout childhood and early adult life in all cases of congenital heart block. Fatal Adams-Stokes attacks occasionally occur in children,[26] and one of our patients died unexpectedly at the age of 5 years, presumably from this cause. Certainly prophylactic pacing in childhood is unnecessary in most, particularly as morbidity associated with pacemakers is more likely to be the result of repeated electrode trauma and displacement of pacing leads caused by growth.[27]

In attempting to assess prognosis and the need for pacing, Moltham and his colleagues[26] suggested that a wide QRS with or without left bundle-branch block was ominous, while a QT interval exceeding 0·43 was considered a serious risk factor predicting the early onset of symptoms.[28] We did not find any significant abnormalities on the electrocardiogram in our patients, apart from a prolonged QT in one. What may be more helpful in defining which patients may require early pacing before the development of symptoms is the application of controlled exercise testing. Taylor and Godfrey[29] studied four patients with congenital heart block on a bicycle ergometer. Two were able to achieve normal maximum work even though they did so without reaching a satisfactorily increased cardiac output and with a very low oxygen content of venous blood. Winkler and his colleagues from Boston[30] subjected 25 children with complete heart block to maximum exercise testing on the treadmill using the Bruce protocol and compared the results with those of 50 normal children and young adults used as controls. Seventeen (68%) out of the 25 with heart block had significant and frequent ventricular ectopics on the electrocardiogram during exercise compared with only one (2%) out of the 50 controls. This finding they concluded could be a bad prognostic factor for possible sudden death. We did not subject any of our patients to exercise testing, but this appears to be a promising single and safe means of helping to assess the need for pacing in asymptomatic patients with congenital heart block. This is nowadays much more relevant, with the striking developments and improvements in reliability of pacemakers over the last few years.

Patients with congenital heart block presenting with symptoms in early infancy require emergency pacing. Accompanying congenital heart disease constitutes an additional risk factor. This was present in 30% of the patients in the international series reported by Michaëlsson and Engle[5] and undoubtedly affected the outcome adversely. It was found in only six (17%) of our 35 patients. Most, however, do not require pacing in childhood, but an increasing number do so from the second decade onward. Life-long supervision is imperative, as most will require a permanent pacemaker before the age of 50 years.

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Absent left atrioventricular connection with right atrium connected to morphologically left ventricular chamber, rudimentary right ventricular chamber, and ventriculoarterial discordance

Problem of mitral versus tricuspid atresia

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SUMMARY Four cases of absent left atrioventricular connection are reported. The observations from these cases have been used to emphasise problems concerning the use of the confusing terms "tricuspid" and "mitral" atresia to describe such hearts. One of the four cases represents a very uncommon condition since the rudimentary chamber was contralateral to the side of the absent atrioventricular connection. The morphology of the conduction system has been elucidated with emphasis given to the surgical implications of these anomalies.

Atrioventricular valve atresia has become the subject of increased interest since the development of innovative surgical treatment.[1] Only recently, however, has the anatomy of these syndromes been clarified with emphasis to the differentiation of an absent atrioventricular connection and an imperforate atrioventricular valve.[2] It has also been pointed out that when one atrioventricular connection is absent, the morphology of the patent atrioventricular valve is highly variable and poorly identifiable. Consequently it has been suggested that it is more accurate to distinguish these cases as absent right or left atrioventricular connection rather than tricuspid and mitral atresia.[2] More recently, however, the advisability of this concept has been questioned.[3] In the light of this correspondence, we report here four pertinent cases with absent left atrioventricular connection. The findings in these hearts strongly support the remarks of one of us in an earlier paper.[4] All the hearts had main ventricular chambers of left ventricular type. Two cases had the rudimentary right ventricular chamber on the same side of the absent connection, the usual pattern. One case, in contrast, had the rudimentary chamber on the opposite side to the absent atrioventricular connection.[5 6] The final case is even more fascinating since the rudimentary right ventricular chamber was more or less directly anterior.

Case reports

CASE 1

The heart was situated in the left hemithorax, with the apex to the left. There was a left aortic arch (Fig. 1a). Atrial situs solitus was present with normal venous connections. The right atrium was enlarged. The left atrium showed an accessory superior chamber into which four pulmonary veins drained. It was obstructed at its junction with the main atrial chamber, which received two large pulmonary veins. The left atrial floor was completely muscular, having no connection with the ventricular mass (Fig. 1b). The atrial septum showed a patent foramen ovale. The ventricular mass was largely made up of a left ventricular chamber. It was connected with the right atrium through an atrioventricular valve of uncertain morphology (Fig. 1c) Two leaflets were tethered by large

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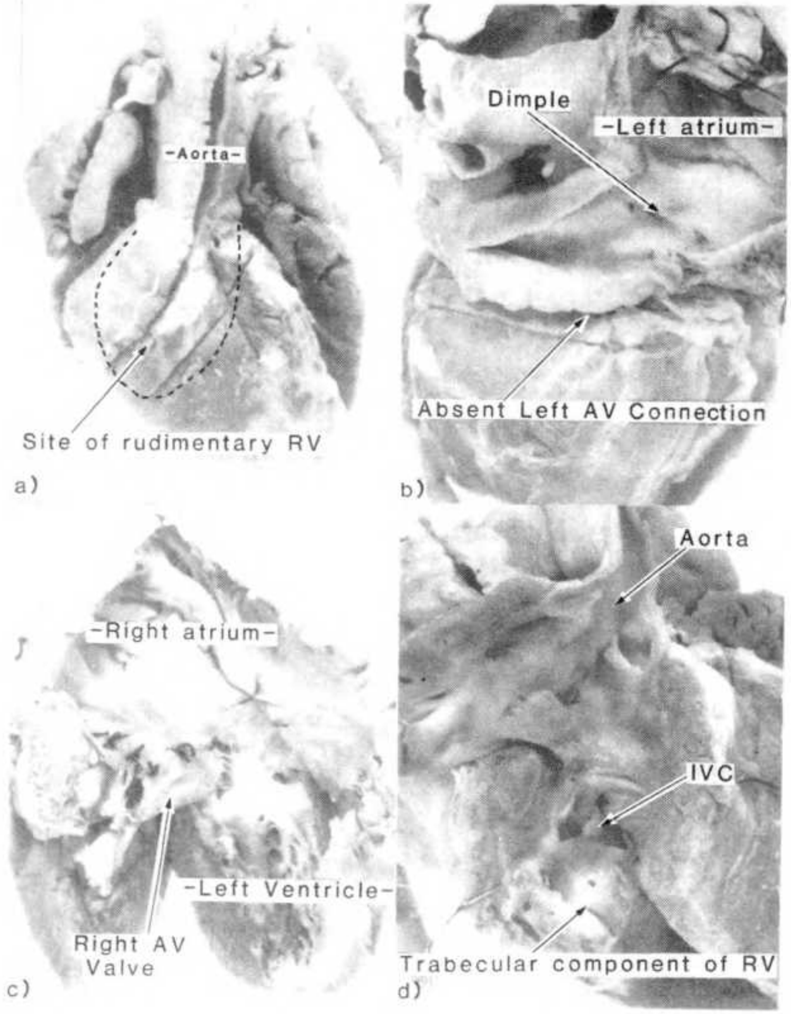


Fig. 1 *The cardiac morphology in case 1. (a) The anterior view of the heart. The dotted line shows the position of the rudimentary right ventricular chamber. (b) The absent left atrioventricular connection. (c) The right atrium connected to a left ventricular chamber. (d) The opened rudimentary right ventricular chamber, the right atrioventricular (AV) valve being seen covering over the interventricular communication (IVC).*

anterior and posterior papillary muscles. The interventricular communication, which looked obstructed since it was covered by the atrioventricular valve mural leaflet, led to a hypoplastic right sided and anterior rudimentary chamber of right ventricular type which showed a prominent trabecular portion and extremely short infundibular segment (Fig. 1d). The aorta arose from the rudimentary chamber, being anterior and to the right of the pulmonary trunk which arose from the main left ventricular chamber. The pulmonary valve was in fibrous continuity with the solitary atrioventricular valve. The ascending aorta and the arch appeared moderately hypoplastic. A persistent ductus arteriosus was present.

Fig. 2 shows a diagrammatic representation of the conduction system as judged from inspection of the heart. The atrioventricular bundle was not in direct relation with the posterior pulmonary outflow tract.

CASE 2

The aortic arch and cardiac apex were to the left (Fig. 3a). Atrial situs solitus with normal venous connections was found. The left atrium had no connection with the ventricular mass. A patent foramen ovale was present. The main left ventricular chamber was connected with the right atrium through an atrioventricular valve of atypical morphology which showed three leaflets (Fig. 3b). A third papillary muscle was attached to the trabecular septum. The interventricular communication was displaced leftwards, leading to a rudimentary chamber of right ventricular type which was mostly on the left (Figs 3a, 3c). The

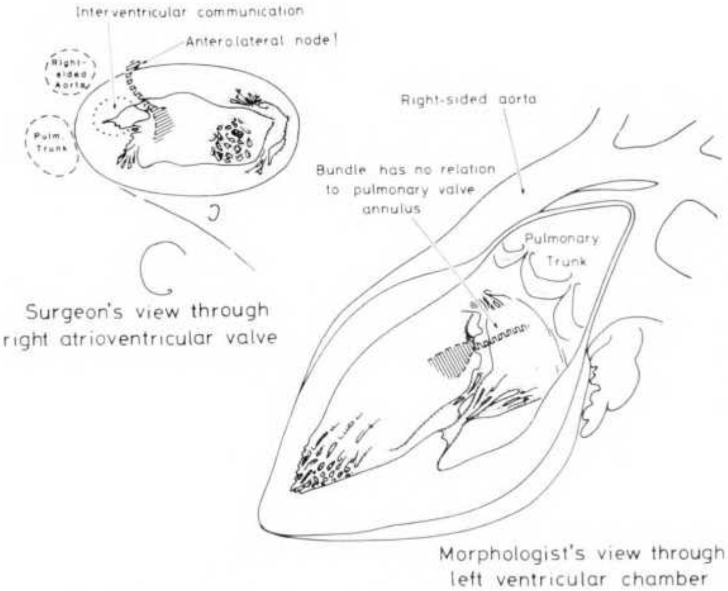

Interventricular communication
Anterolateral node!
Right-sided Aorta
Pulm. Trunk
Surgeon's view through right atrioventricular valve
Right-sided aorta
Bundle has no relation to pulmonary valve annulus
Pulmonary Trunk
Morphologist's view through left ventricular chamber

Fig. 2 *A representation of the conduction tissue disposition in case 1. The main drawing shows the site of the atrioventricular conduction axis as would be seen through an incision in the left side of the left ventricular chamber (compare with Fig. 3d). The inset shows the course of the bundle relative to the right atrioventricular and pulmonary valves as would be seen by the surgeon approaching via the right atrium.*

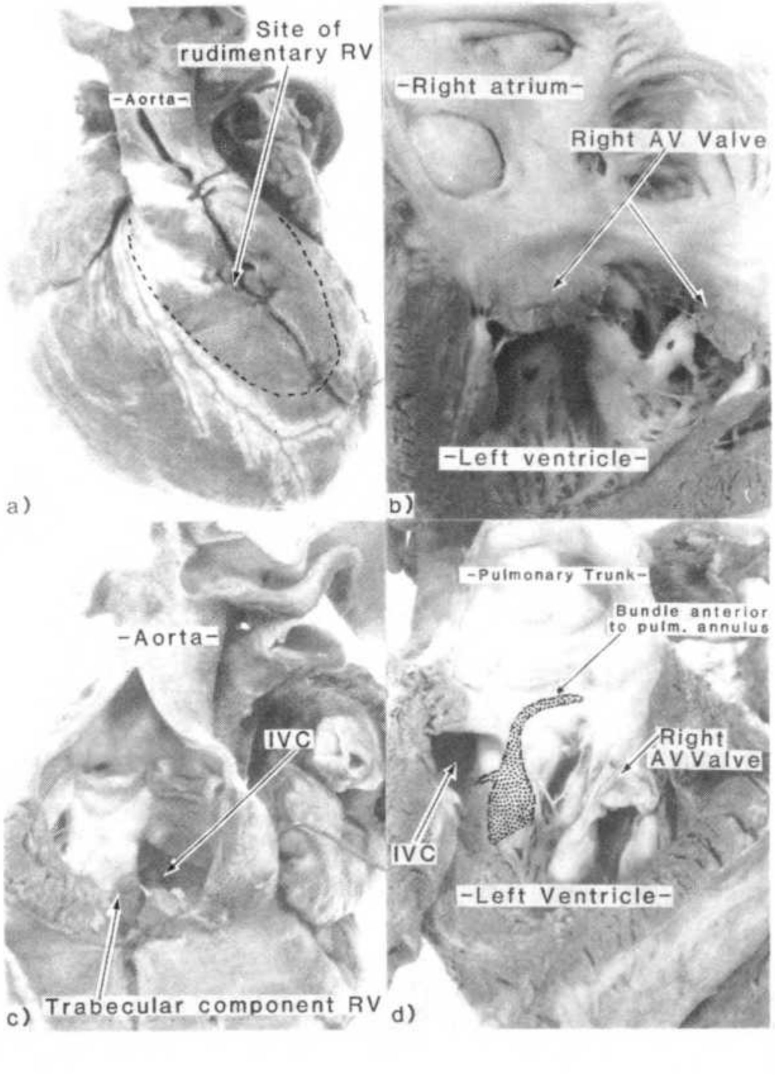


Fig. 3 *The cardiac morphology of case 2. (a) The anterior view of the heart. Despite the left sided position of the rudimentary right ventricular chamber (dotted lines) the aorta is to the right of the pulmonary trunk. (b) The right atrioventricular valve connecting right atrium to a left ventricular chamber. (c) The opened rudimentary right ventricular chamber. (d) The main left ventricular chamber opened through a left sided incision. The site of the conduction tissues has been superimposed (compare with Fig. 2).*

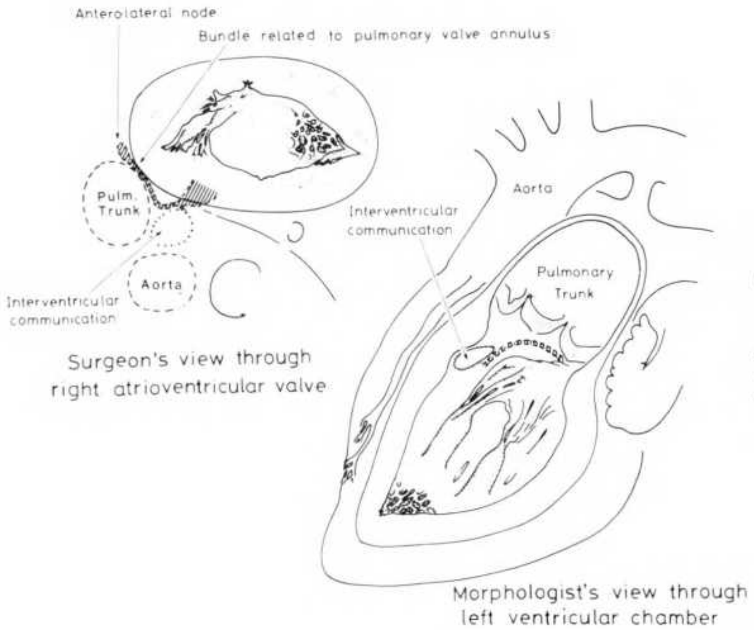

Anterolateral node
Bundle related to pulmonary valve annulus
Pulm. Trunk
Aorta
Interventricular communication
Surgeon's view through right atrioventricular valve
Aorta
Interventricular communication
Pulmonary Trunk
Morphologist's view through left ventricular chamber

Fig. 4 *Representation of the conduction tissue disposition in case 2. The main drawing shows the view as illustrated in Fig. 3d while the inset gives the surgeon's view as seen through the right atrioventricular valve.*

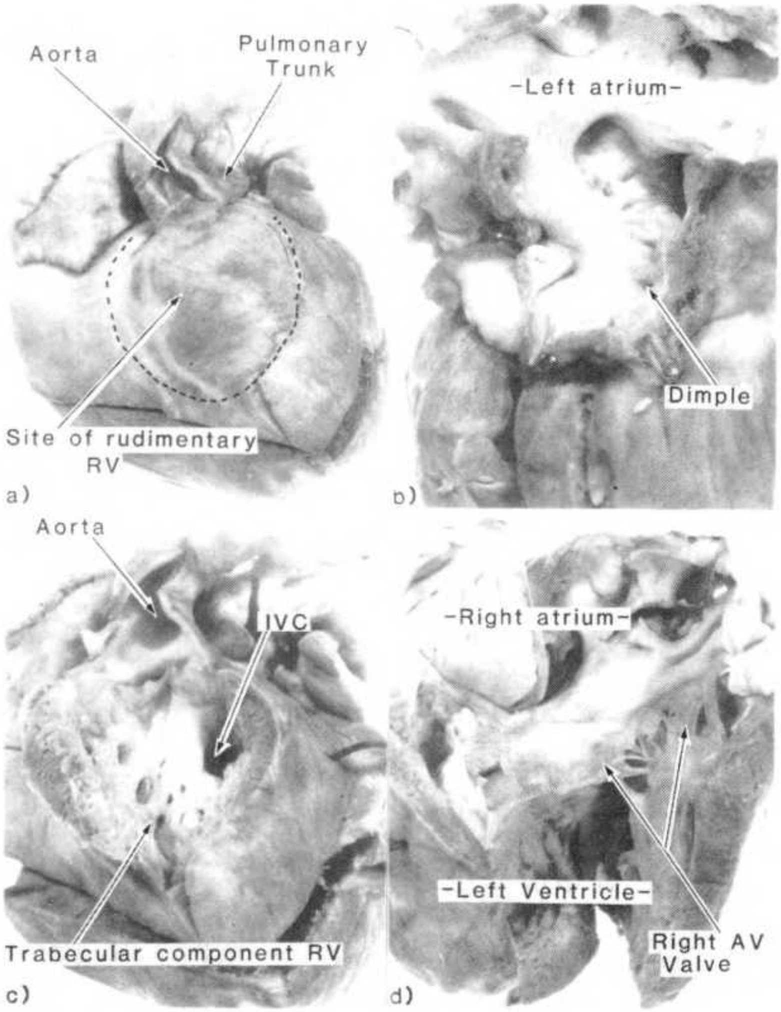


Fig. 5 *The cardiac morphology of case 3. (a) An anterior view with the directly anterior position of the rudimentary right ventricular chamber marked. (b) The absent left atrioventricular connection. (c) The opened rudimentary chamber. (d) The morphology of the right atrioventricular valve.*

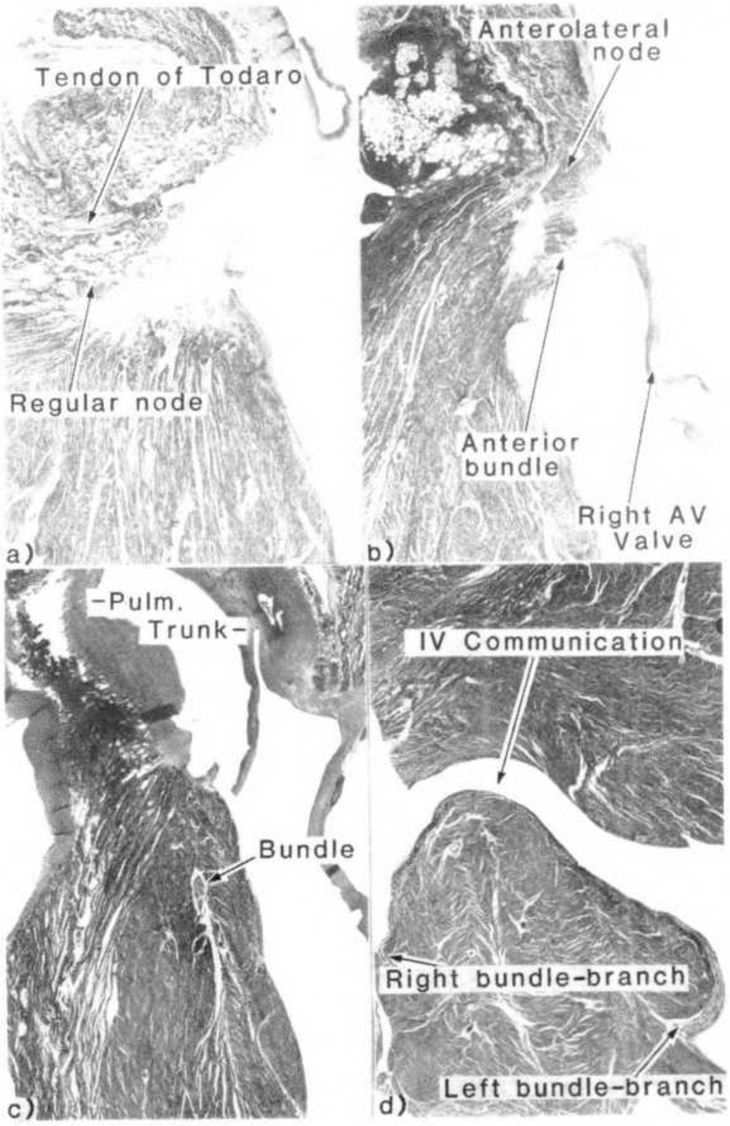


Fig. 6 *The conduction tissues from case 4. (a) The regular atrioventricular node at the apex of the triangle of Koch which makes no connection with the ventricular conduction tissues. (b) The anterolateral node giving rise to the penetrating bundle. (c) The bundle running intramyocardially around the anterior quadrant of the pulmonary trunk. (d) The bundle-branches to either side of the interventricular septum.*

rudimentary chamber showed a prominent trabecular portion and a very short infundibular segment, giving origin to a normally sized aorta, there being no obstruction of the interventricular communication (Fig. 3c). Despite the leftward position of the rudimentary chamber, the aorta was found to be on the right and anterior to the pulmonary trunk (Fig. 3c). The pulmonary trunk arose from the main left ventricular chamber in fibrous continuity with the patent atrioventricular valve (Fig. 3b). A ductus arteriosus was also present in this case.

In Fig. 4 the course of the conduction tissue is shown as judged from the gross examination of the heart. Note that the non-branching bundle encircles the subpulmonary outflow tract.

CASE 3

There was left sided position of the aortic arch and cardiac apex (Fig. 5a). Atrial situs solitus with normal venous drainage was encountered. The left atrioventricular connection was absent (Fig. 5b). The atrial septum showed evidence of balloon septostomy. The right atrium communicated with the main left ventricular chamber through an atrioventricular valve which showed two leaflets (Fig. 5c). Anterior and posterior papillary muscles were present. A good sized interventricular communication was found to be anterior and to the left of the ventricular mass leading to a rudimentary chamber of right ventricular type which showed a prominent trabecular component and very short infundibular segment (Fig. 5d). The rudimentary chamber was more or less anterior in relation to the main chamber; the rudimentary trabecular component, however, was unequivocally on the right. The aorta arose from the rudimentary chamber and was anterior and to the right of the pulmonary trunk (Fig. 5a). The pulmonary trunk, taking origin from the main chamber, was in fibrous continuity with the patent atrioventricular valve. Both great arteries were of normal size and a persistent ductus arteriosus was present.

The conduction tissue disposition was as illustrated in Fig. 4.

CASE 4

The aortic arch and cardiac apex were to the left. Atrial situs solitus with normal venous connections was present. Absence of the left atrioventricular connection was found, with a patent foramen ovale on the atrial septal surface. The right atrium connected with the main left ventricular type chamber through an atrioventricular valve which was of mitral morphology, having paired papillary muscles. The interventricular communication was to the left of the ventricular mass and was somewhat restrictive. It led to a left sided rudimentary chamber of right ventricular type which showed the same prominent trabecular component and a very short infundibular segment as encountered in the three previous cases. The aorta, arising from the rudimentary chamber, was anterior and to the left of the pulmonary trunk. Aortic arch and isthmal hypoplasia were found. The pulmonary trunk arose from the main chamber with the atrioventricular valve. Persistent ductus arteriosus was also present.

In this case the entire right atrioventricular junction was sectioned to show the disposition of the conduction tissues. The regular node in the atrial septum made no contact with the ventricular myocardial tissues, being a blind-ending structure (Fig. 6a). Instead, an anomalous anterolateral node was found (Fig. 6b) which gave rise to a penetrating atrioventricular bundle. This penetrated to the right of the pulmonary trunk. A long non-branching bundle (Fig. 6c) then encircled the anterior quadrant of the pulmonary valve before descending into the right margin of the interventricular septum, where it branched on its left ventricular aspect well below the septal crest (Fig. 6d). A right bundle-branch then penetrated through the septum into the rudimentary right ventricular chamber while the left bundle-branch ramified on the left ventricular surface. The overall distribution of atrioventricular conduction tissue was as shown in Fig. 4.

Discussion

In the past it has been customary to classify the atrioventricular valve atresias simply as tricuspid atresia and mitral atresia. Only recently has the full anatomy of the lesions been discussed with regard to the clinical ability to differentiate an absent atrioventricular connection from an imperforate atrioventricular connection.[2] In the light of these findings, it has been suggested that, when one atrioventricular connection is absent, it is preferable to distinguish absence of the right sided and left sided connections rather than nominating the conditions as tricuspid or mitral atresia. This is because, since the essence of the anomaly is absence of the atrioventricular connection, it can never be known with certainty whether, had the connection developed, it would have been guarded by a mitral or a tricuspid valve.

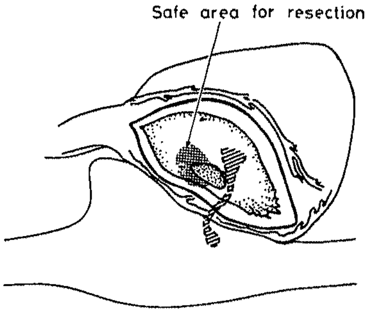
In the hearts herein described, the right atrium communicated always with a left ventricular chamber and always there was ventriculoarterial discordance. The difference in the four cases related only to the position of the rudimentary right ventricular chamber. In two cases the chamber was left sided, as usually described in this entity, but in one it was right sided and in the other it was directly anterior. All this is vital information in the light of the recent suggestion by Gittenberger-de Groot and Wenink[3] that all hearts with valve atresia should be distinguished as having mitral or tricuspid atresia according to the ventricular architecture present. They indicated that ventricular architecture could be deduced from knowing the ventricular relations, and then from this information the nature of the atretic valve could be inferred. If we apply this process to our cases, then presumably a diagnosis of "mitral atresia" would be made in the case with right sided rudimentary chamber and "tricuspid atresia" in the cases with left sided rudimentary chamber. But what of the case with directly anterior chamber? Furthermore, if we examine the case with right sided rudimentary chamber (presumed d-bulboventricular loop), one would expect the solitary atrioventricular valve to be of tricuspid morphology. Instead, we find it to be more reminiscent of mitral morphology. Conversely, considering the second case with a left sided rudimentary chamber (presumed l-loop), a solitary mitral valve would be expected. Surprisingly, the valve present is reminiscent of a tricuspid valve.

What this shows is that the conclusion that one can categorise all valve atresias as mitral or tricuspid from inferential evidence concerning ventricular architecture is palpably incorrect. In the cases we studied, architecture could certainly not be predicted with accuracy from knowledge of the ventricular relations. It may be possible to make a more accurate judgement knowing the morphology of the atrioventricular valve present, but this information is unlikely to be available to the clinician. Thus, the concept offered by Gittenberger-de Groot and Wenink[3] may be of value to the morphogeneticist, but is unlikely to be of great help to the clinician, since it is not based upon morphological features as observed by the clinician. We submit that it is far more accurate, more comprehensive, and more useful simply to describe absence (or atresia) of the right or left atrioventricular connection and then to describe the chamber combinations present. This gives the information required by the clinician, and at the same time gives all the evidence required by the morphogeneticist to make deductions concerning the nature of the atretic connection if this is so desired.

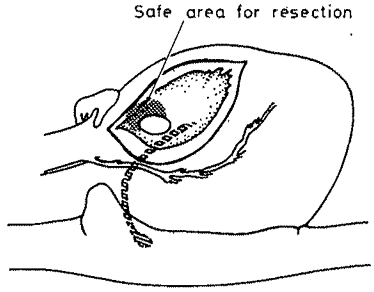
From this discussion, it can be seen that in no way do we deny the value of the looping concept promoted by Van Praagh *et al.*[7] as a mechanism for the understanding of congenital heart disease. Indeed, Weinberg, working with Van Praagh and others,[8] has shown more recently how it is essential to describe the loop (ventricular architecture) in those rare cases where it is incongruous for a given atrial situs and atrioventricular connection. Our own group[9] has further emphasised the need for describing the ventricular architecture in hearts with ambiguous atrioventricular connection. But the feature of all these hearts (that is those with biventricular atrioventricular connections) is that the architecture can be readily identified in terms of the imaginary placement of the palmar surface of the observer's hand on the septal surface of the morphologically right ventricle with the thumb in the inlet, the wrist in the trabecular component, and the fingers in the outlet.[10] In this way, right hand (typical for the normal) and left hand (typical for "ventricular inversion") patterns can be easily appreciated. It is much harder to determine ventricular architecture when the atria connect to only one ventricular chamber (univentricular atrioventricular connection), particularly when the ventricle is of left ventricular or indeterminate morphology. This is because the inlets in such hearts are either connected to the same ventricle, or else one inlet is absent. It is not therefore possible to "anchor one's thumb" when trying to "place the imaginary hand" on the septal surface of the morphologically right ventricular chamber (or, in the indeterminate hearts, to find a septum). Because of this we find it difficult to apply the "loop convention" in hearts with univentricular atrioventricular connection such as presently described. Moreover, we can see neither a need nor any relevance, from the clinician's or surgeon's view point, to attempt so to identify the "loop' or the imagined morphology of the absent valve. The first case presently described deserves particular comment since it represents a very uncommon condition. Usually absence of one atrioventricular connection is associated with presence of the rudimentary ventricular chamber on the same side as the absent connection. Two cases, however, were reported by Quero,[5 6] with the rudimentary chamber on the opposite side to the absent connection. Subsequently a few additional cases have been described[11-13] and angiocardiographic documentation has been reported.[14] In his original report, Quero indicated that the right sided position of the rudimentary right ventricular chamber pointed to the existence of mitral atresia, again using the loop to predict the nature of absent connection. He then suggested that this was most unusual, since with mitral atresia it would be expected for the left ventricular chamber to be hypoplastic and the right ventricular chamber to be the main ventricular chamber. He expressed this in terms of normal development, rather than hypoplasia, of the topographically homologous ventricle. At that time, however, the distinction had not been made between atrioventricular valve atresias with biventricular and univentricular atrioventricular connections. If the cases described had possessed imperforate valve membranes, Quero's comments[5 6] would be entirely appropriate. But in fact the cases had absence of an atrioventricular connection. When an atrioventricular connection is absent and the other atrium connects to a main ventricular chamber, the relation of the rudimentary ventricular chamber is an independent factor. So, when the left connection is absent and the right atrium connects to a left ventricular chamber, the rudimentary right ventricular chamber is usually left sided, but as we have seen may be right sided or even directly anterior. When the right atrioventricular connection is absent with similar chamber connections, then usually the rudimentary right ventricle is right sided, but it may be directly anterior or even to the left. In hearts with univentricular atrioventricular connection to a left ventricular chamber, it has been emphasised that, though there is a basic disposition of the atrioventricular conduction system, the precise course of the non-branching atrioventricular bundle within the ventricles is dependent upon the position of the rudimentary chamber.[15-17] The findings encountered in the cases here reported further support these remarks. In the first case with right sided rudimentary chamber there was an anterior node from which a very short bundle arose going down immediately along the main chamber aspect of the trabecular septum.[18] In contrast, in the cases with left sided rudimentary chambers, there was an anterior node, in the same position as in case 1, from which an elongated atrioventricular bundle coursed towards the trabecular septum in close proximity to the posterior pulmonary outflow tract.

These morphological features are of considerable surgical significance. If surgical "correction" is to be attempted in hearts such as these, it will probably be done using a Fontan type procedure. The position of the node will not be a major feature, since always it will be necessary to preserve the right atrioventricular orifice. It is the relation of the conduction tissues to the interventricular communication which is paramount. If there is ventriculoarterial discordance, as is usually the case, it may be necessary to enlarge this communication. If there is ventriculoarterial concordance, a rare happening,[5] it will be necessary to close the communication if an atrioventricular conduit is to be constructed.[19] Whichever option is attempted, it must be known that the branching bundle is carried on the left ventricular aspect of the septum away from the septal crest, and that the non-branching bundle descends on to the right margin of the foramen. The rim of the foramen formed by the outlet septum never harbours conduction tissue, and the left margin is also a safe area for resection. These rules hold good whatever the position of the rudimentary right ventricular chamber (Fig. 7). It must be emphasised, however, that we speak of the right and left margins of the interventricular communication relative to its anatomical position. These margins may not always be perceived as being in right sided or left sided position, this depending entirely upon the approach taken by the surgeon.

Finally, the rare occurrence of ventriculoarterial concordance[5] in these anomalies is worthy of emphasis. This arrangement permits the pulmonary venous blood to be switched into the main left ventricular chamber via an intra-atrial baffle. The rudimentary chamber can then be opened and the interventricular communication closed, a valved conduit being placed between the right atrium and the rudimentary right ventricular chamber. This procedure, which represents a modification of the Fontan operation, has been successfully performed in one case.[19] The reason for incorporating the rudimentary chamber into the pulmonary circuit is the possibility of growth and development of the chamber. Such a modified Fontan procedure could be performed even in cases in which the rudimentary chamber is left sided, providing there is ventriculoarterial concordance. If ventriculoarterial discordance is present, however, as in the cases here reported, a baffle procedure and the classical atriopulmonary Fontan bypass would be the only possible option other than combining an atrioventricular bypass with an arterial switch procedure.[20]



Right-sided rudimentary RV chamber



Left-sided rudimentary RV chamber

Fig. 7 *Diagram illustrating the vital relation of the atrioventricular conduction axis to the interventricular communication as seen by the surgeon approaching through the rudimentary right ventricular chamber. Note that the position of the rudimentary chamber does not alter the basic disposition of the conduction axis, and that the safe area for widening the communication is the same in both arrangements.*

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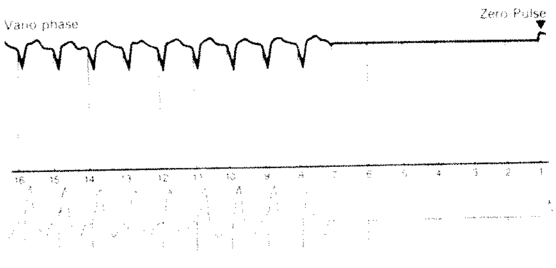

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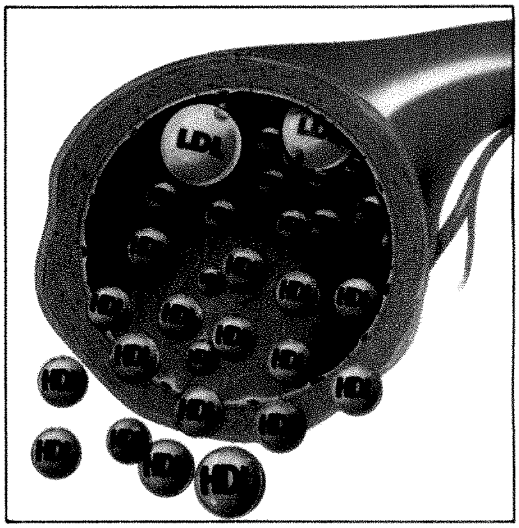

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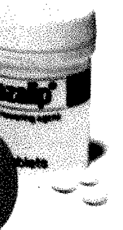

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Total anomalous pulmonary venous connection
Repair using deep hypothermia and circulatory arrest in 44 consecutive infants

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SUMMARY Forty four consecutive infants aged from 3 days to 10 months underwent repair of total anomalous pulmonary venous connection using deep hypothermia with circulatory arrest. There were eight (18%) early hospital deaths. Using multivariate analysis no significant association could be shown between early mortality and age or weight at operation, preoperative pulmonary or systemic pressure, and preoperative condition for patients undergoing operation during the most recent five year period. Late pulmonary venous obstruction developed in four (11%) of the survivors and all of these patients died.

Total anomalous pulmonary venous connection is a relatively uncommon cardiac malformation representing less than 1% of all congenital cardiac anomalies.[1 2] Without surgical treatment, the mortality within the first year of life is high,[3] and those who survive may develop progressive pulmonary vascular disease.[4 5] Early surgical intervention is therefore indicated in the majority of patients. Successful surgical correction was first reported by Muller in 1951[6] and subsequently others described their experience in the surgical management of this lesion, using either hypothermia with inflow occlusion,[7] or standard cardiopulmonary bypass.[8 9] It is only with the adoption of deep hypothermia and circulatory arrest, however, that satisfactory results have been achieved in infancy.[10–13]

In this paper, we review our experience during the last 12 years of single stage correction of total anomalous pulmonary venous connection in infancy using this latter technique.

Patients and methods

During the period January 1970 to December 1981, 44 consecutive infants under one year of age with total anomalous pulmonary venous connection underwent single stage surgical correction at the Royal Liverpool Children's Hospital, using deep hypothermia and circulatory arrest. Four infants who were operated on in 1970 and 1971 using standard cardiopulmonary bypass and previously reported[13] are not included in this report. One further case also included in the previous report,[13] with infracardiac total anomalous pulmonary venous connection occurring as part of a complex malformation associated with the asplenia syndrome is excluded since the operation was an attempt at palliation rather than correction.

The patients are grouped according to the site of pulmonary venous connection (Fig. 1). Twenty-two patients had supracardiac total anomalous pulmonary venous connection and nine had infracardiac total anomalous pulmonary venous connection. The group of eight patients with intracardiac total anomalous pulmonary venous connection includes six with drainage entirely to the coronary sinus and two with drainage direct to the right atrium. Five patients had a mixed type of total anomalous pulmonary venous connection. In four, part of the left upper lobe drained into the innominate vein, while the remaining veins entered the coronary sinus. The fifth patient had both upper lobe veins entering the superior vena cava while the lower lobe veins entered the right atrium via a common venous channel.

There were 22 male and 22 female patients ranging in age from 3 to 312 days (mean 77 days) at the time of operation. The weight at operation varied from 2·3 kg

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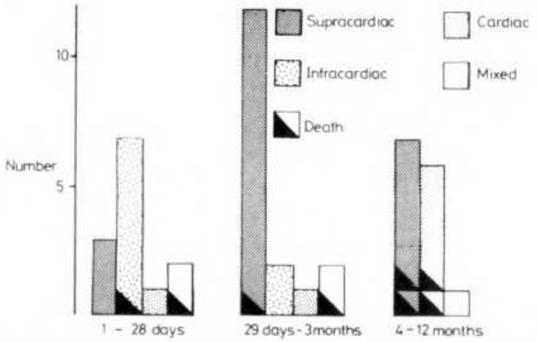

Fig. 1 *Age at operation and anatomical type in 44 infants with total anomalous pulmonary venous connection.*

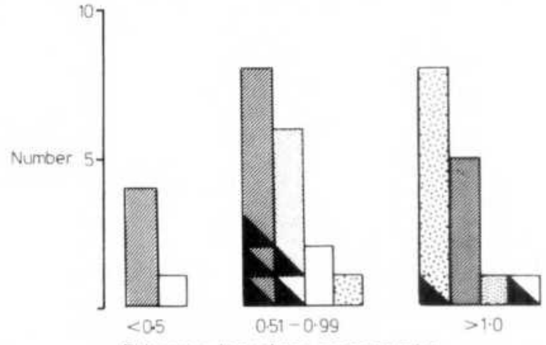

Fig. 2 *Preoperative pulmonary to systemic pressure ratio and anatomical type in 37 infants with total anomalous pulmonary venous connection. Key as for Fig. 1.*

to 8·7 kg (mean 3·9 kg). One patient was known to have a ventricular septal defect and the ductus arteriosus was patent in a further 14 patients. Balloon septostomy was performed at the time of diagnostic catheterisation in nine patients: four with a supracardiac connection, three with drainage to the coronary sinus, and two with mixed total anomalous pulmonary venous connection.

PREOPERATIVE CONDITION

Each patient was assigned retrospectively to one of three groups according to the clinical condition at the time of diagnosis. Group 1 consisted of four infants whose symptoms were well controlled on medical treatment and who underwent operation electively at a mean interval of 122 days (range 95 to 155 days) from the time of presentation. In group 2 there were 27 infants with severe symptoms but no acute deterioration in whom operation seemed advisable without undue delay. These infants underwent surgery two to 54 days (mean 13 days) from the time of diagnosis. Group 3 consisted of 13 critically ill infants who underwent emergency operation at a mean interval of 2·8 days from the time of diagnosis (range less than one to eight days). Five patients in this group had supracardiac and eight had infracardiac total anomalous pulmonary venous connection. Eight of these patients were ventilated electively before operation because of respiratory failure. Critical preoperative status was correlated significantly with young age and with raised pulmonary and lowered systemic pressures at the time of cardiac catheterisation ($p = 0.05$ to 0·01 in each case; t tests, confirmed by Mann-Whitney tests).

All cases were operated on using deep hypothermia induced with core cooling, and total circulatory arrest using techniques described previously.[13 14] For patients with supra- and infracardiac total anomalous pulmonary venous connection a left anterolateral thoracotomy with transternal extension was used.[15] Patients with cardiac or mixed types of total anomalous pulmonary venous connection were repaired through a median sternotomy. In three most recent patients with mixed total anomalous pulmonary venous connection predominantly to the coronary sinus the operation suggested by Van Praagh *et al.*[16] for total anomalous pulmonary venous connection to the coronary sinus was used.

Preoperative measurements of pulmonary and systemic pressure were made in 37 patients and the pulmonary to systemic pressure ratios for each anatomical group are shown in Fig. 2.

STATISTICAL ANALYSIS

Seven factors were selected as having a possible influence on early mortality: anatomical type, age and weight at operation, preoperative condition, preoperative Pco_2 (without assisted ventilation), preoperative pulmonary and systemic pressures, and the duration of circulatory arrest. Complete data were available for 29 consecutive patients operated on during the most recent five year period. These data were tabulated and the *Statistical package for the social sciences*[17] was used for cross-tabulation, unpaired Student's t test and discriminant analysis predicting early death or survival. Where necessary, transformation to a logarithmic scale was performed to normalise data before using Student's t test.

Results

EARLY MORTALITY

Eight infants (18%) died within 30 days of the operation. During the most recent five year period, 29 consecutive infants (11 supracardiac, eight infracardiac, seven cardiac, and three mixed) have undergone operation, with four early deaths (14%), compared with four early deaths among 15 infants (27%) during the preceding seven years. This difference is not statistically significant. Two of the deaths in the earlier period were the result of avoidable technical errors at the time of operation.

For the 29 patients undergoing operation during the most recent five year period, no significant association could be established between early death and anatomical type, age or weight at operation, preoperative condition, pulmonary or systemic pressures, Pco_2, or duration of circulatory arrest. None of these variables was significantly different for early deaths as compared with other cases (unpaired Student's t test confirmed by Mann-Whitney rank sum test). Nor was any pattern discernible among the four early death cases on any two dimensional plot of any pair of continuous variables except in the case of the age/weight plot where they lay very closely on a straight line. The probability of early death, computed from a linear function on the logit scale by using the generalised linear interactive modelling package,[18] did not depend significantly on any of the above mentioned variables. Linear discriminant analysis between the early deaths and the remaining patients using logarithmic transformations of age, weight, pulmonary and systemic pressure, and duration of circulatory arrest was also ineffective in predicting early death. During this period early death appeared to be a random event not clearly connected with any of the variables studied, either individually or in combination.

LATE RESULTS

Four patients developed pulmonary venous obstruction, all within three months of the initial operation and all subsequently died. Postoperative cardiac catheterisation data on these patients are summarised in the Table. Case 1 underwent a second operation three months after the initial procedure. The orifices of three of the four pulmonary veins were found to be partly obstructed by intimal proliferation. An angioplastic procedure was performed to enlarge the pulmonary veins but the infant died four months later, with clinical evidence of reobstruction of the pulmonary veins. Case 2 was readmitted one month after the first operation. He deteriorated rapidly after investigation and died before a second operation could be performed. Consent for a necropsy was refused. Case 3 had total anomalous pulmonary venous connection to the coronary sinus. At the second operation the opening between the coronary sinus and the left atrium was severely stenotic with thickening of the tissue surrounding this ostium and shrinkage of the Dacron patch placed at the mouth of the coronary sinus. The original operation was revised but the patient died suddenly two months later. At necropsy the inlet of the coronary sinus to the left atrium was widely patent, but the four pulmonary veins entered the apex of the coronary sinus via a single stenotic orifice of less than 4 mm diameter. Case 4 had drainage of the pulmonary veins direct to the right atrium. He died before a second operation could be performed and at necropsy it was found that the right pulmonary veins were totally occluded by shrinkage and thickening of the original Dacron baffle used to redirect pulmonary venous blood into the left atrium.

The 32 longer term survivors have been reviewed

Table *Postoperative cardiac catheterisation data in 11 patients*

Case No.	*Anatomical type*	*Interval after operation (mth)*	*Pressures (mmHg)*		*Pulmonary to systemic flow ratio*	*Comment*
			Pulmonary	*Systemic*		
1	Supracardiac	3	100	65	1	Pulmonary venous obstruction; reoperation; died
2	Infracardiac	1	65	120	1	Pulmonary venous obstruction; died
3	Cardiac	3	80	75	1	Pulmonary venous obstruction; reoperation; died
4	Cardiac	2	90	75	1	Pulmonary venous obstruction; died
5	Supracardiac	59	21	100	2	Residual ASD; successful operation
6	Supracardiac	16	78	84	1·8	Residual VSD; successful operation
7	Infracardiac	1	35	80	1	Transient pericardial effusion; good result
8	Cardiac	13	36	80	1	Good haemodynamic result; atrioventricular block
9	Cardiac	12	28	100	1	Good result
10	Cardiac	26	23	110	1	Good result
11	Mixed	3	28	95	2·2	Residual ASD; awaiting reoperation

ASD, atrial septal defect; VSD, ventricular septal defect.

regularly with a follow up ranging from three months to 10 years (mean 5·1 years). One child (case 5, Table) required a second operation to close a residual atrial septal defect and a second (case 6, Table) has had a second operation to close a ventricular septal defect. A further five patients have been investigated postoperatively (Table). Four have a good haemodynamic result but one has atrioventricular block and one had a transient pericardial effusion at the time of investigation. Two of these patients were investigated because of a slight suspicion on clinical grounds that pulmonary venous obstruction was developing but these suspicions were unfounded. Pulmonary venous obstruction has not been identified in any patient as a later postoperative complication. The last patient (case 11, Table) has a residual atrial shunt after repair of a mixed type of total anomalous pulmonary venous connection and will need a second operation in the future.

The remaining patients are clinically well with no abnormal signs in the cardiovascular system other than wide splitting of the second heart sound and mild cardiomegaly on chest *x*-ray.

Discussion

Before 1970, the surgical mortality for correction of total anomalous pulmonary venous connection in infancy was significantly higher than in older patients and some authors regarded young age as a major factor in determining early mortality.[19] During the past decade, improved results have been achieved particularly in infants under 1 year of age.[11–13 20–22] In these series, young age at operation has not been confirmed as a risk factor and our present results substantiate this view. During the 12 year period reviewed, there were no deaths among five patients operated on during the first week of life showing that even the youngest patients can be corrected successfully. Though we were unable to show a correlation between preoperative condition and early mortality this is only likely to be the case if the operation is performed with an appropriate degree of urgency. We agree with the view expressed by many authors[11 12 20 21] that any delay in the effective surgical treatment of symptomatic infants, particularly when pulmonary venous return is obstructed, may result in a higher operative mortality rate.

Surgical mortality in the patients reported by Clarke *et al.*[12] and Turley *et al.*[20] was most closely related to the anatomical type of total anomalous pulmonary venous connection present. During our most recent experience no such correlation was present with survival of all three patients with mixed total anomalous pulmonary venous connection. It should be noted, however, that these patients had a relatively simple type of mixed total anomalous pulmonary venous connection predominantly to the coronary sinus. In more complex types a higher mortality might be expected.[21] It is interesting that the anatomical type carrying the highest mortality in the series of Clarke *et al.*,[12] Turley *et al.*,[20] and Hammon *et al.*[22] (infracardiac) carried the lowest mortality among our patients. Conversely, we have experienced a relatively high early mortality among patients with the intracardiac type of the anomaly, a defect which in other hands[11 12 20] carries a low mortality. The number of deaths in each series, however, is small and many deaths were related to factors individual to each patient rather than specific for a particular anatomical type. For example, two deaths in the present series and two deaths among the patients reported by Whight *et al.*[11] were mainly the result of avoidable technical errors unrelated to the particular anatomical type present. Reviewing the combined recent experience of the groups in Auckland, Boston, and Birmingham, Katz *et al.*[21] concluded that anatomical type was not a determinant of early mortality except in the case of patients with the complicated mixed type of total anomalous pulmonary venous connection. Our results show that an early mortality of less than 15% should be expected in patients with the supra- and infracardiac types. Others[11 12 20] have shown that a similar or lower mortality can be achieved with total anomalous pulmonary venous connection to the right atrium or coronary sinus.

Though late mortality after correction of total anomalous pulmonary venous connection is low,[23] in many recently reported series there has been significant mortality and morbidity associated with the development of pulmonary venous obstruction.[11 20 24] Four (11%) of the 36 hospital survivors in our series developed this complication, all within three months of the original operation. In one case, the main reason for obstruction appeared to be related to shrinkage and thickening of a synthetic Dacron patch, but in two cases, one with supracardiac drainage and one with the coronary sinus type, obstruction developed at the orifices of the pulmonary veins at a site remote from any suture line. The cause of obstruction in the fourth case was not determined. Though pulmonary venous obstruction has been described in patients with total anomalous pulmonary venous connection before surgical treatment,[3] there was no evidence of this in any of our patients. Similar findings have been reported by other authors. Both Turley *et al.*[20] and Fleming *et al.*[24] reported cases of infradiaphragmatic total anomalous pulmonary venous connection developing pulmonary venous obstruction at a site proximal to the original anastomosis. In the study of Whight *et al.*[11] three patients with total anomalous pulmonary venous connection to the coronary sinus developed pulmonary venous obstruction, caused in one case by thickening of a pericardial patch and in two further cases by partial obliteration of the ostia of the pulmonary veins by fibrosis. Surgical treatment of pulmonary vein obstruction is difficult[11 20] and the problem may recur even after apparently successful reoperation.[20] Its occurrence is unpredictable and though it appears to be more common after repair of the infradiaphragmatic type, it is by no means confined to that group.

Several approaches have been used to gain optimal exposure of the anomalous venous channels in supra- and infracardiac total anomalous pulmonary venous connection. Throughout the 12 year period, we have used the left anterolateral thoracotomy advocated by Roe.[15] It has been suggested that aortic cannulation might prove to be difficult using this approach and that cannulation of the descending aorta might be necessary.[15] With trans-sternal extension of the incision, however, we have not found this to be the case. In our experience, the left anterolateral thoracotomy gives excellent exposure of the left atrium and common pulmonary vein and facilitates the construction of the largest possible anastomosis in spite of the small size of the left atrium in this anomaly.[25 26] If necessary, the incision can be extended onto the left atrial appendage which is usually of relatively normal size.[26] We have not found it necessary during this 12 year period to enlarge the size of the atrial cavity in any patient either by using a patch or by moving the interatrial septum to the right. No problems with kinking of the anastomosis have been encountered and pulmonary venous obstruction at the suture line has not been recognised as a late complication in any patient with these anatomical types of total anomalous pulmonary venous connection.

Several authors[11 22 25] have published their findings at cardiac catheterisation carried out one to six years after operation for total anomalous pulmonary venous connection. Their findings show normal or near normal right and left ventricular and left atrial volumes, with normal right ventricular pressures in the majority of asymptomatic survivors. Unexpected major residual defects were not identified. In view of these encouraging reports, we have studied our postoperative patients only when specific clinical indications were present.

Conventional repair of total anomalous pulmonary venous connection to the coronary sinus involves incising the margin of the coronary sinus and carrying the incision back through the foramen ovale into the left atrium. A large patch is then used to roof over the combined orifice of the coronary sinus and fossa ovale. An alternative procedure was suggested by Van Praagh *et al.*[16] in 1972. Though the procedure was originally devised to avoid damage to internodal conduction pathways, its main advantage appears to be the avoidance of prosthetic material within the atrium of a small infant. In view of the problems encountered after patch shrinkage both in our patients and those reported by Whight *et al.*,[11] this advantage appears to be considerable. We have used this method in three recent cases with mixed type total anomalous pulmonary venous connection predominantly to the coronary sinus and intend to use it more extensively in the future.

The role of balloon atrial septostomy in the management of the infant with total anomalous pulmonary venous connection remains a subject for debate. Left heart filling in this condition is entirely dependent on a right to left atrial shunt, and the atrial septum may be a site of obstruction even in patients with no pressure gradients between left and right atrium.[26] Balloon septostomy has therefore been recommended for all infants with total anomalous pulmonary venous connection as a means of palliating the symptomatic infant.[27 28] Patients with pulmonary venous obstruction are unlikely to be benefited. The procedure, however, may be helpful in infants in whom the pulmonary venous return is unobstructed, pulmonary artery pressure is less than half systemic, and postponement of operation for a short period is desired. Whight *et al.*[11] have drawn attention to a possible disadvantage of balloon septostomy in patients with total anomalous pulmonary venous connection to the coronary sinus in whom the Van Praagh technique[16] is to be used for repair, in that closure of the atrial septum may be easier if the fossa ovale is intact. We have used balloon atrial septostomy in nine patients in an attempt to improve left heart filling preoperatively. Though it has been suggested that septostomy may be difficult in total anomalous pulmonary venous connection,[27] using biplane screening facilities, the procedure has not been accompanied by any morbidity in our patients. We do not, however, regard this procedure as a substitute for urgent surgical treatment in the majority of patients.

Our experience with the management of infants with total anomalous pulmonary venous connection during the past 12 years suggests that the best results are obtained when referral to a specialised paediatric cardiac unit is made as soon as the diagnosis is suspected, preferably during the first weeks of life. Since surgical mortality is not correlated with young age, operation should be performed on an emergency or semi-emergency basis as the patient's condition demands. Unnecessary delay is likely to lead to acute deterioration particularly when pulmonary venous obstruction is present. The long term results and excellent health of the surviving children are just reward to the medical and surgical team who accept the considerable challenge which these seriously ill infants present on admission to hospital.

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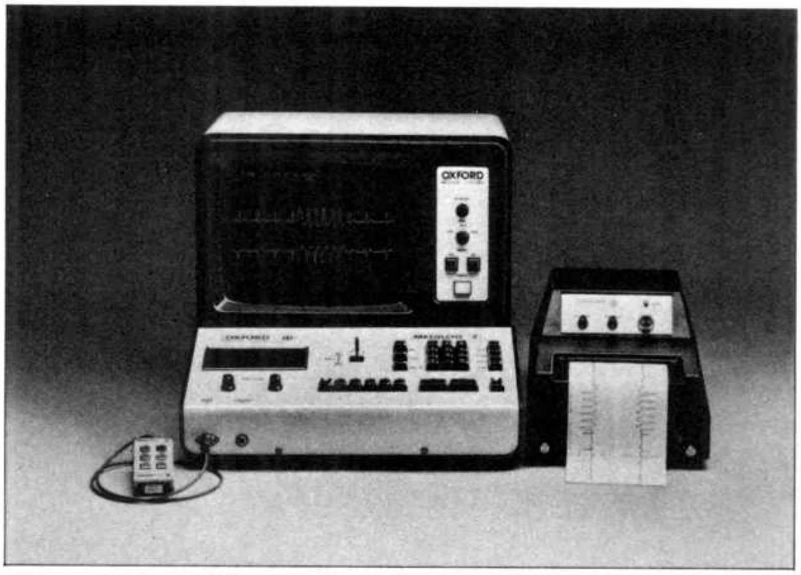

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Routine radionuclide techniques in evaluation of patients with suspected coronary heart disease

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SUMMARY Myocardial scintigraphy with thallium-201 and electrocardiogram-gated left ventriculography with technetium-99m labelled red blood cells were applied in four groups of subjects: 25 with no signs or symptoms of cardiovascular disease (group 1), 28 with a "false" positive exercise electrocardiogram (group 2), 14 with angina pectoris and normal coronary angiograms (group 3), and 43 with angina pectoris and fixed coronary artery stenoses (group 4). In groups 1 and 4 the radionuclide findings were in accordance with clinical and invasive measurements. In groups 2 and 3 the most important finding was the lack of increase in left ventricular ejection fraction during exercise in about half of these subjects (even a decrease in 25%), indicating subnormal myocardial reserve. The additional finding of pathological myocardial biopsies in four of these patients suggests that asymptomatic ST depression in patients with normal coronary angiograms may in some cases represent an early, preclinical sign of cardiomyopathy.

Radionuclide techniques added to conventional evaluation such as exercise testing and angiographic studies have provided valuable additional information concerning myocardial function in the study of patients with overt coronary heart disease.[1–3]

Among the most widely used radionuclide tests are (1) the study of myocardial perfusion during exercise and in the redistribution phase using thallium-201 (^{201}Tl), and (2) the study of left ventricular function at rest and during exercise using technetium-99m (^{99m}Tc) labelled red cells.

An increasing number of patients with mild or atypical angina pectoris or with ST depression without symptoms found during screening exercise electrocardiographic testing are currently being referred to our hospital for further evaluation. A question of major interest is whether the above mentioned radionuclide techniques can provide more accurate diagnostic data in such patients,[4 5] and also provide information unobtainable from conventional invasive techniques. With these questions in mind we have applied the two tests mentioned above in patients with angina or a positive exercise electrocardiogram response discovered prospectively, but in whom coronary angiography disclosed normal findings.

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Subjects and methods

Included in the study were 110 subjects, who all gave informed consent. None had valvular or congenital heart disease. They are subdivided into four groups (see below). Groups 1 and 2 are derived from a prospective cardiovascular survey group of 2014 apparently healthy middle aged men. All 115 men fulfilling predetermined criteria of having suspected coronary heart disease were offered coronary angiography to confirm or exclude this suspicion. The details about that survey (including angiographic findings) have been published elsewhere.[6] The latter two groups (3 and 4) include patients referred to our department for evaluation of incapacitating angina pectoris.

GROUP 1:25 NORMAL SUBJECTS

Group 1 was selected randomly from the cardiovascular survey among men fulfilling the following criteria on two examinations performed seven years apart: no symptoms or signs of coronary heart disease or other heart disease, normal blood pressure, normal findings on x-ray film of the heart and lungs, normal resting electrocardiogram, and a negative response to a near maximal exercise test (heart rate of at least 90% of predicted maximal heart rate) without abnormalities in the electrocardiogram.[6] The mean age was 54·6 years (SD 5·5 years).

GROUP 2:28 "FALSE" POSITIVE EXERCISE ELECTROCARDIOGRAM

These 28 men had a "false" positive exercise electrocardiogram during the primary study (described above); that is significant ST depression, but normal coronary arteries on the angiogram.[6] This group originally included 36 men. At follow-up after seven years, two had died suddenly, three had congestive heart failure, two had diseases of the locomotor system which made exercise testing impossible, and one had moved to another area. The remaining 28 men from this group were re-examined and all had similar ST depression on their exercise electrocardiogram to that recorded seven years earlier. A second angiographic study—during which myocardial biopsies were obtained—was performed in four of these 28 men in an attempt to clarify further their disease.[7–9] The mean age of this group was 56·1 years (SD 5·1 years).

GROUP 3: 14 PATIENTS WITH ANGINA PECTORIS AND NORMAL ANGIOGRAMS

This group represents a consecutive series of 14 patients (six women and eight men) referred to hospital because of incapacitating angina and whose coronary angiograms were normal. Three had significant ST depression on their exercise electrocardiograms and 11 had a normal exercise electrocardiogram. Mean age was 46·9 years (SD 6·6 years).

GROUP 4: 43 PATIENTS WITH ANGINA PECTORIS AND FIXED CORONARY ARTERY STENOSES

These patients represent a consecutive series of 43 patients (four women and 39 men) with severe angina and pathological coronary angiograms. All had at least one stenosis ≧70% of the vessel area in one of the major epicardial arteries. Thirty-two had had a myocardial infarction. Eighteen had significant ST depression on the exercise electrocardiogram, 11 had stress tests with normal electrocardiographic findings, and in 14 we could draw no conclusions on exercise testing because of the effects of drug treatment. Mean age was 55·1 years (SD 7·1 years).

Methods

EXERCISE TESTING

This was started at 50 watts in groups 3 and 4 and at 100 watts in groups 1 and 2, and the load was increased stepwise by 50 watts every six minutes. Endpoints of the exercise tests were: angina, ST depression ≧3 mm, severe dyspnoea, general fatigue/exhaustion, arrhythmias, or any combination of these factors. Chest-head leads CH1–7 were used during exercise and 12 lead electrocardiograms before, and for five minutes after exercise. A positive exercise electrocardiogram was defined as one with ST depression ≧1·5 mm 0·08 s from the J point in CH leads 2–7, or 1·0 mm in leads I, II, aVF, aVL, or V2–7, irrespective of whether the ST segment was upward- or downward-sloping or horizontal.[6]

Coronary angiography was performed as described by Judkins.[10]

RADIONUCLIDE PROCEDURES

An identical exercise test procedure was used for the ^{201}Tl perfusion imaging and radionuclide ventriculography, and was similar to the above mentioned procedure except for the fact that during the radionuclide studies the patients were exercised supine with the trunk immobilised. Cardiac scintigrams were obtained with a GE scintilation camera (Maxicamera 400 T) with hardware 2:1 zoom. The camera was interfaced to an Intertechnique cine 330 data system.

PERFUSION SCINTIGRAPHY

60 mli ^{201}Tl was injected in an antecubital vein when peak load was reached, and 90 seconds before termination of the exercise. Immediately after exercise and five hours later images were obtained in three views by collecting 200 000 counts per image. Areas showing diminished uptake in the immediate post-exercise period were scrutinised for differences in the pattern five hours later. Reversible ischaemia was said to be present in patients in whom perfusion defects were observed immediately after exercise and in whom the uptake was normal five hours later. Myocardial scarring was thought to be present when perfusion defects were observed immediately after exercise, persisting unaltered five hours later.

RADIONUCLIDE VENTRICULOGRAPHY

This was performed as multiple gated acquisition at equilibrium after in vivo labelling of erythrocytes with 900 mli of ^{99m}Tc pertechnetate. The detector was located in the 40° left anterior projection with 15° caudal tilt. In list mode 1 500 000 counts were stored together with the electrocardiogram. Composite cardiac cycles (16 frames) were computer generated. Left ventricular end-diastolic and end-systolic contours were operator outlined. Left ventricular ejection fraction was calculated as end-diastolic counts − end systolic counts divided by end-diastolic count after background subtraction. An increase in left ventricular ejection fraction from resting to exercise values of less than 5% was considered as pathological.[11 12] Regional wall motion abnormalities were assessed by cinematic display of the composite cardiac cycles, and by construction of stroke volume images, paradox images, and regional ejection fraction images.

Results (see Fig.)

GROUP 1: NORMAL SUBJECTS

All 25 subjects had normal perfusion according to the

^{201}Tl study. Left ventricular ejection fraction increased from 68·4% (SD 6·5) at rest to 76·0% (SD 7·1) during exercise ($p < 0.01$). Only one man (62 years old) increased his left ventricular ejection fraction by less than 5% during exercise (=4%). The remaining 24 men increased theirs by 6 to 19%. There was no association between age and increase in left ventricular ejection fraction during exercise (data not shown). Abnormal wall motion could neither be detected at rest nor during exercise in any of the normal subjects.

GROUP 2: "FALSE" POSITIVE EXERCISE ELECTROCARDIOGRAM

The 28 men with a "false" positive exercise electrocardiogram all showed normal myocardial perfusion at rest and during exercise. Left ventricular ejection fraction was 67·0% (SD 8·1) at rest and showed a moderate increase to 70·3% (SD 11·3) during exercise ($p < 0.05$). In 15 of the 28 men, however, left ventricular ejection fraction increased by less than 5%, and in seven of these 15 the left ventricular ejection fraction actually decreased during exercise. No abnormal wall motion could be detected.

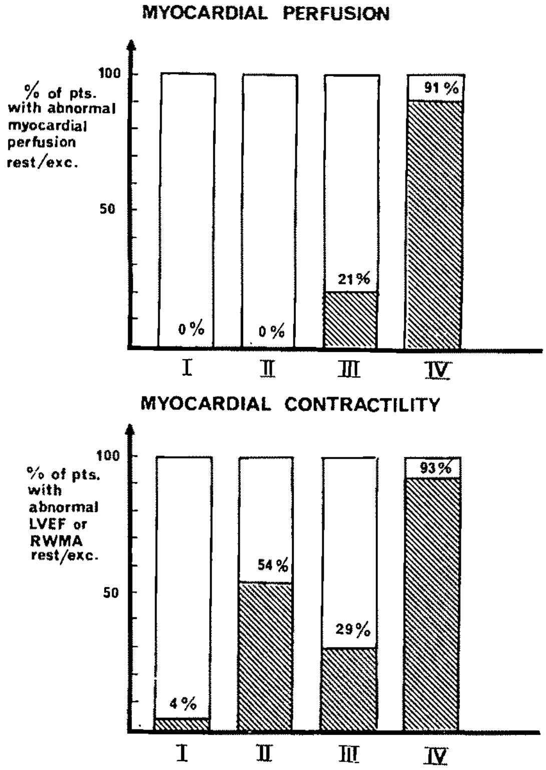

Fig. *Myocardial perfusion and contractility pattern in four groups of patients studied with* ^{201}*Tl scintigraphy and* ^{99m}*Tc ventriculography. See text for details of groups. LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormalities.*

The myocardial biopsies showed nonspecific changes with atrophy and hypertrophy of the muscle fibres in three patients and oedema and interstitial fibrosis in one patient. All had end-diastolic pressures greater than 12 mmHg at rest and three greater than 20 mmHg after angiography. Left ventricular ejection fraction was unaltered during exercise in all four patients.

GROUP 3: ANGINA PECTORIS, NORMAL CORONARY ANGIOGRAMS

In 11 of the 14 patients normal myocardial perfusion was found both at rest and during exercise. Two presented regional perfusion defects during exercise with normal perfusion five hours later, whereas one showed regional perfusion defect during exercise as well as five hours later. The resting left ventricular ejection fraction, 64·0% (SD 7·9), increased significantly during exercise to 71·2% (SD 11·6; $p < 0.01$). In four patients the increase was less than 5% (including two with a decrease in left ventricular ejection fraction during exercise). Regional wall motion abnormalities were not seen in this group. Perfusion defects and/or subnormal left ventricular ejection fraction response during exercise were found in five in this group.

GROUP 4: ANGINA PECTORIS WITH FIXED CORONARY ARTERY STENOSES

Thirty-nine of the 43 patients had pathological ^{201}Tl images, either as myocardial scarring (32) or reversible ischaemia (26), or both. Of the 32 with a previous myocardial infarction, 31 were shown to have myocardial scarring on ^{201}Tl scintigraphy. The left ventricular ejection fraction decreased from 46·3% (SD 15·9) to 41·8% (SD 15·3) during exercise ($p < 0.01$). In 38 of 43 patients the left ventricular ejection fraction either decreased or increased by less than 5%, that is only five in this group showed the normal increase in left ventricular ejection fraction during exercise. Regional wall motion abnormalities were found in 17. All 43 from this group had at least one pathological radionuclide test finding.

Discussion

The diagnosis of coronary heart disease is made in most patients admitted to hospital from clinical symptoms and resting and exercise electrocardiographic findings, and can be verified by coronary angiography. Under such circumstances radionuclide techniques, as shown by ^{201}Tl scintigraphy and ^{99m}Tc ventriculography, indicate disease which accords with the angiographic and clinical findings. The inclusion of such patients in the present report as well as the inclusion of men thought to be normal (those in group 1) was done in order to document the reliability of the radionuclide techniques in our hands. Our findings agree closely with those of other investigators.[1-3] Thus, the radionuclide studies disclosed disease in all 43 patients with angiographically documented coronary heart disease. The diagnostic considerations, however, proved to be more ambiguous among the patients with normal angiograms from groups 2 and 3. The knowledge of the presence or absence of significant coronary artery disease in such patients has prognostic as well as therapeutic implications. Thus, the presence of symptom-free coronary heart disease, angiographically verified after the finding of a pathological exercise electrocardiogram,[6] has recently been shown to carry a grave prognosis.[13] On the other hand, normal coronary angiograms in similar patients have been reported to indicate a favourable prognosis.[14 15]

One side effect of cardiovascular surveys, and in particular surveys that include electrocardiographic exercise testing, is the identification of a large number of subjects with pathological exercise electrocardiograms and/or mild or atypical angina.[6 15] Radionuclide techniques should be a valuable tool for further diagnostic evaluations in such cases. If the ^{201}Tl studies only had been applied, however, one could easily have reached the conclusion that nothing was wrong with the men from group 2, for example. The ^{99m}Tc studies of left ventricular function, however, disclosed significant abnormalities in a high number of subjects from group 2 as well as from group 3. As presented above, several subjects showed less than a 5% increase in left ventricular ejection fraction (or even a decrease) during exercise. An increase in left ventricular ejection fraction of less than 5% has been said to indicate a pathological response,[5 11 12] a view which is similar to ours among the 25 normal subjects. The subnormal response in subjects from group 2, and also to a lesser extent for patients from group 3, cannot be explained as a physiological ageing phenomenon since we did not find any association between age and left ventricular ejection fraction response.[16] Our findings of impaired myocardial function in subjects from groups 2 and 3 are in agreement with other recent reports.[17 18]

As mentioned above, two men from the original group of 36 men had died suddenly, and in addition three had developed congestive heart failure. In four men from group 2 nonspecific pathological myocardial changes were found in endomyocardial biopsies together with raised end-diastolic pressures, that is findings consistent with a diagnosis of cardiomyopathy.[7 8] In the light of these combined findings it is conceivable that the ST depression in the exercise electrocardiograms as well as the subnormal increase in left ventricular ejection fraction during exercise reflect signs of cardiomyopathy in an early phase in several cases.

The demonstration of coronary artery spasms as a probable cause of coronary artery narrowing associated with angina pectoris has challenged the traditional view that only fixed coronary artery stenoses may cause a reduction in blood flow sufficient to cause transient myocardial ischaemia.[19 20] In the present study reversible myocardial ischaemia related to possible coronary artery spasm was rare, since it was only suggested in two patients from group 3 and none from group 2. This is in agreement with some and in conflict with other reports of similar groups of patients.[18 21 22] The differences may be explained by differences in patient selection and also by the fact that we did not use drugs that could provoke coronary artery spasm.[23]

In conclusion, the application of radionuclide techniques in subjects with asymptomatic ST depression on exercise electrocardiogram and in patients with angina pectoris can help in identifying patients who probably have coronary heart disease or other heart diseases. Patients with pathological radionuclide findings should be followed closely and receive appropriate treatment. On the other hand, subjects with normal radionuclide findings should be considered healthy and be reassured of a good prognosis.

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Br Heart J 1982; **48**: 260–4

Reversible ischaemia of right ventricle detected by exercise thallium-201 scintigraphy

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SUMMARY Exercise and redistribution thallium-201 imaging is commonly used for the detection and evaluation of left ventricular ischaemia and infarction. The right ventricle is frequently visualised after stress and sometimes on redistribution images. The visualisation of the right ventricle at rest is thought to be abnormal and is suggestive of pressure or volume overload of the right ventricle, either a result of pulmonary hypertension or secondary to left ventricular dysfunction. Using stress and delayed ^{201}Tl imaging we have shown reversible left and right ventricular ischaemia and fixed left ventricular perfusion defects in two patients with multivessel coronary artery disease and left ventricular dyskinesia caused by prior myocardial infarction. Judging by the rarity of this finding as well as taking into consideration ^{201}Tl kinetics, it is suggested that reversible right ventricular ischaemia after exercise may only be detected in patients with coronary artery disease who have severely compromised ventricular function. This finding may have therapeutic and prognostic significance.

Though thallium-201 (^{201}Tl) exercise and redistribution imaging are accepted methods of detecting reversible left ventricular ischaemia resulting from coronary artery disease,[1] visualisation of right ventricular ischaemia is uncommon, particularly in patients undergoing exercise ^{201}Tl imaging. The right ventricle not only has a smaller muscle mass but has less blood flow.[2] Thallium-201 has a low photon energy (69–83 KeV) so that tissue attenuation is high, and the target to background ratio is low. During exercise testing in normal subjects, however, the right ventricle can usually be visualised because the myocardial extraction fraction of ^{201}Tl is increased. This produces a high target to background ratio and both the ventricles are visualised despite the ratio between the right and left ventricles remaining unchanged. When delayed imaging is used (two to four hours), the target to background ratio falls and only the left ventricle remains visible.

The right ventricle is usually visible in exercise ^{201}Tl images in normal and compromised hearts and the right ventricle may also be observed in the left anterior oblique view in early redistribution images in normal patients.[3] Visualisation of the right ventricle on scans performed at rest, however, is thought to be abnormal and usually implies pressure or volume overload of the right ventricle, such as in pulmonary hypertension[4] and right heart failure secondary to left ventricular failure.[5-7]

We have shown reversible right ventricular ischaemia associated with left ventricular dysfunction and reversible left ventricular ischaemia in two patients with coronary artery disease.

Patients and methods

EXERCISE TESTING

Maximal, symptom-related treadmill exercise testing was carried out using a modified Balke's protocol and leads CM5 and CC5 were continuously monitored (Marquette Electronics), as described elsewhere.[8]

THALLIUM-201 SCINTIGRAPHY

Thallium-201 imaging was carried out using the same exercise procedure as above, and 2 mCi of ^{201}Tl was injected intravenously through a cubital vein at peak exercise. The patient then continued for a further 60 seconds at a reduced workload. Imaging was carried out in three views (anterior, 45 degrees left anterior oblique, and left lateral views) seven to 10 minutes after exercise, and redistribution imaging was carried out four hours later.[8] A high resolution collimator was

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used to collect 300 000 counts in each view. The counts from the abdomen were shielded with a lead sheet. The data were stored on a computer (Gamma 11, Digital) for later analysis.

The data both "raw" and digitised were reported by three trained observers with good agreement. The computer was used to remove 40% of the lower threshold and nine point smoothing was carried out.

A positive identification of a perfusion defect was made semiquantitatively when there was 50% or more reduction of counts in the ventricular wall as compared with a region of maximal myocardial count density containing about 5000 counts in a selected region of interest. Quantitative analysis of the relative lung uptake of ^{201}Tl was also carried out.[9 10]

MULTIPLE GATED BLOOD POOL ANGIOGRAPHY

Gated blood pool angiography was carried out using 20 mCi of technetium-99m (^{99m}Tc) labelled red blood cells. Three million counts were recorded in the anterior and left anterior oblique views (40 degrees LAO with a 10 degree caudal tilt). Data were stored on a hard disc (Gamma 11, digital) and analysed using the method of Maddox *et al.*[11] to obtain global ejection fractions and to assess regional left ventricular wall motion.

CONTRAST ANGIOGRAPHY

Contrast left ventricular angiography and coronary arteriography were carried out using the Judkins technique and multiple views were obtained.

Case reports

CASE 1

A 46 year old man presented with exertional angina nine months after an anterior myocardial infarction. Exercise testing showed 3 mm ST segment elevation over leads presenting with "Q" waves in CM5 and CC5. The patient stopped at four minutes because of chest pain. Thallium-201 scintigraphy showed an enlarged heart, increased lung uptake of ^{201}Tl, an anterior wall perfusion defect (fixed), and reversible perfusion defects of the inferior wall and of the inferior part of the right ventricle (Fig. 1). Multiple gated blood pool angiography showed apical dyskinesia, anterior akinesia, and septal hypokinesia of the left ventricle. The calculated ejection fraction was 19%. Coronary arteriography disclosed complete proximal left anterior descending coronary artery occlusion (100%), 90% narrowing of the proximal right coronary artery with diffuse disease, and a nondominant left circumflex coronary artery with less than 50% narrowing. There was no established collateral circulation. Left ventricular angiography confirmed the findings of the radionuclide angiogram and a dyskinetic anteroapical aneurysm was demonstrated.

CASE 2

A 41 year old man with a history of a previous anterior myocardial infarction 14 months ago presented with mild exertional angina. Exercise testing showed ST segment depression in CM5 and CC5 (2 mm in CC5) after nine minutes and the test was discontinued because he developed dyspnoea and slight chest pain. Thallium-201 imaging showed a fixed anterior wall perfusion defect. Reversible ischaemia was noted in the posterolateral left ventricular wall and in the free right ventricular wall (Fig. 2). Increased lung uptake of ^{201}Tl was also shown. Radionuclide angiography disclosed akinesia of the anterior and apical left ventricular wall. The calculated resting ejection fraction was 26%. Subsequent coronary arteriography showed complete occlusion of the left anterior descending coronary artery (100%) distal to a large marginal

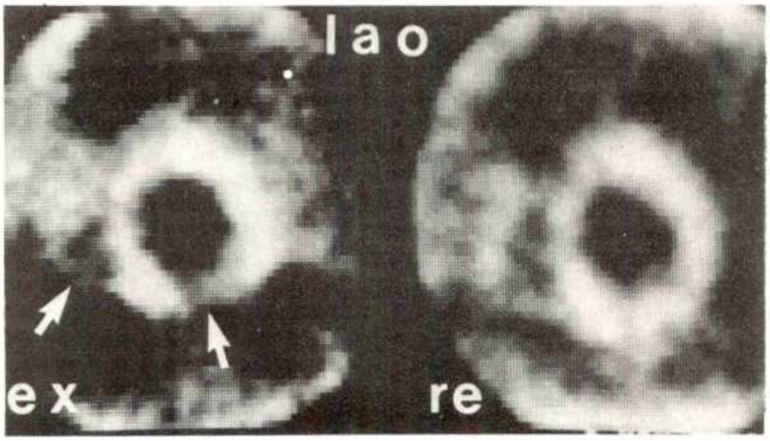

Fig. 1 *LAO-45° ^{201}Tl images after exercise testing (ex) and redistribution (re) four hours after exercise. The exercise image shows photon deficient areas in the inferior wall of the left ventricle and the inferior part of the free right ventricle (arrows). The redistribution image shows normalisation of the exercise perfusion defects and a persistent right ventricular image, which is an abnormal finding on delayed images and is suggestive of right ventricular overloading.*

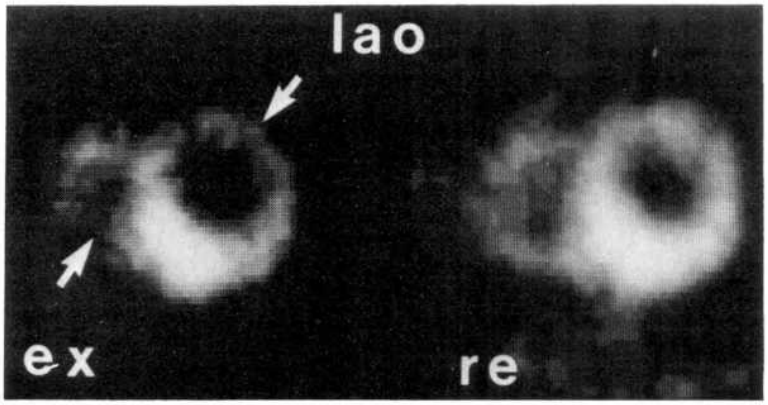

Fig. 2 *LAO-45° ^{201}Tl images after exercise testing (ex) and redistribution (re) four hours after exercise. The exercise scan shows perfusion defects in the lateral wall and in the inferior segment of the right ventricle (arrows). These defects return to normal on delayed images (re), but the persistent right ventricular image is suggestive of right ventricular overloading.*

branch which had a 70% stenosis at its origin. The occluded left anterior descending artery filled retrogradely from its stenosed marginal branch. The left circumflex coronary artery had an irregular lumen with a 70% stenosis at the middle and the right coronary artery was normal. Contrast left ventricular angiography confirmed the presence of an anteroapical aneurysm.

Discussion

Necropsy studies have shown that the posterior left ventricular wall is always involved in right ventricular infarction and that there is a 50 to 75% chance of right ventricular involvement with inferior and inferoseptal left ventricular infarctions.[12] Candell-Riera *et al.*[13] using lead RV4 during exercise, echocardiography, haemodynamic studies, and ^{99m}Tc myocardial infarction imaging detected right ventricular involvement in more than 50% of patients with acute inferior wall infarction. Thus, one may extrapolate from these data and postulate that exercise-induced right ventricular ischaemia may occur in association with reversible ischaemia of the inferior wall (right coronary artery territory) and/or lateral and posterolateral walls (left coronary artery territory) of the left ventricle. The demonstration, however, of reversible right ventricular ischaemia using exercise and delayed redistribution imaging with ^{201}Tl will only be possible when the right ventricle becomes visible either because of an increase in right ventricular overload secondary to left ventricular dysfunction or because of the presence of pulmonary hypertension.

In a recent report, Brachman *et al.*[14] described reversible ischaemia of the right ventricle in two patients with multiple vessel disease. Early redistribution scans (40 minutes) rather than delayed post-exercise imaging (four hours) were reported to be of value for demonstrating reversible right ventricular ischaemia, and it was thought that this finding would improve the sensitivity of detecting right coronary artery disease.[14] We have shown reversible right ventricular ischaemia in two patients, however, using only the post-exercise and the delayed (four hours) scans. Furthermore, right ventricular ischaemia was demonstrated in the presence of a normal right coronary artery (case 2). Our patients not only showed evidence of depressed left ventricular function at rest but developed indications of exercise-induced left ventricular dysfunction and heart failure as evidenced by exercise-induced ST segment elevation in one (case 1)[7] and increased lung uptake of ^{201}Tl in both patients.[9 10 15 16]

The vascular supply of the right ventricle is usually from the right coronary (90%) and from the left circumflex coronary (10%) arteries.[13] Slutsky *et al.*,[17] using exercise radionuclide angiography, showed a reduction of right ventricular ejection fraction in patients with either right or left coronary artery disease. They suggested that this might be secondary to left ventricular dysfunction associated with ischaemia of the left and right ventricles.

Wackers *et al.*,[18] using a dual isotope technique, found that 37·5% of patients with acute inferior wall infarction concentrated ^{99m}Tc-stannous pyrophosphate (^{99m}Tc-pyp) in the right ventricle, whereas ^{201}Tl imaging identified left ventricular perfusion defects in all. This report,[18] however, did not mention the number of patients who had increased right ventricular concentration of ^{201}Tl. Sharpe *et al.*[19] reported similar findings using gated radionuclide angiography, ^{99m}Tc-pyp, and M-mode echocardiography, and found that right ventricular function was impaired in patients with acute inferior infarction in whom ^{99m}Tc-pyp concentrated in the right ventricle. The limitation of ^{99m}Tc-pyp is that it can only be used with moderate success in acute infarction and not in patients such as we have investigated. Sugrue *et al.*[20]

described an attractive method for calculating selective right ventricular ejection fraction using ultra short lived ^{81m}Kr (T½ = 13 s) given as an intravenous infusion. Using this method it is feasible that stress studies may be carried out in order to detect right ventricular ischaemia. Quantitative myocardial blood flow measurements to the right ventricle may be obtained by using single photon emission tomography and intraventricular injection of microspheres.[21]

In our institution we have not previously noted right ventricular ischaemia while assessing early redistribution in patients with coronary artery disease.[8] We feel that the early visualisation of the right ventricle, in the two cases reported by Brachman *et al.*,[14] was probably the result of increased right ventricular overload secondary to exercise-induced left ventricular dysfunction in patients with multiple vessel disease.

Demonstration of reversible right ventricular ischaemia may be the result of either right or left coronary artery disease. The presence of associated reversible regional left ventricular ischaemia may be helpful in identifying the diseased coronary artery responsible for the dominant vascular supply to the right ventricle. In the presence, however, of established collateral circulation ^{201}Tl perfusion defects may not be visualised in patients with significant coronary occlusion.[22]

Though the concept of detecting right ventricular ischaemia with ^{201}Tl is an attractive one, the physical characteristic of ^{201}Tl and the difference between right and left ventricular blood flow make this a difficult application.

The presence of reversible right ventricular ischaemia on exercise and redistribution ^{201}Tl images implies that either the right or left coronary artery is stenosed and that there is either pressure or volume loading of the right ventricle. In the presence of both left and right ventricular ischaemia one may be able to identify the coronary artery lesion responsible for right ventricular ischaemia. This finding may have therapeutic and prognostic significance, since occlusion of the jeopardised coronary artery is likely to produce a biventricular failure which is more resistant to treatment. When considering medical treatment, afterload and preload reducing agents may help to improve ventricular function.

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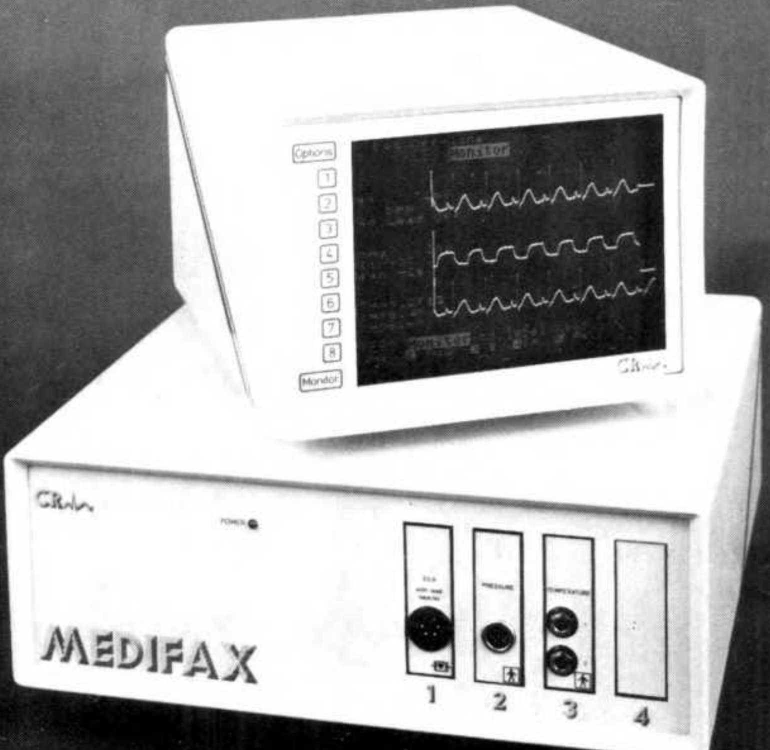

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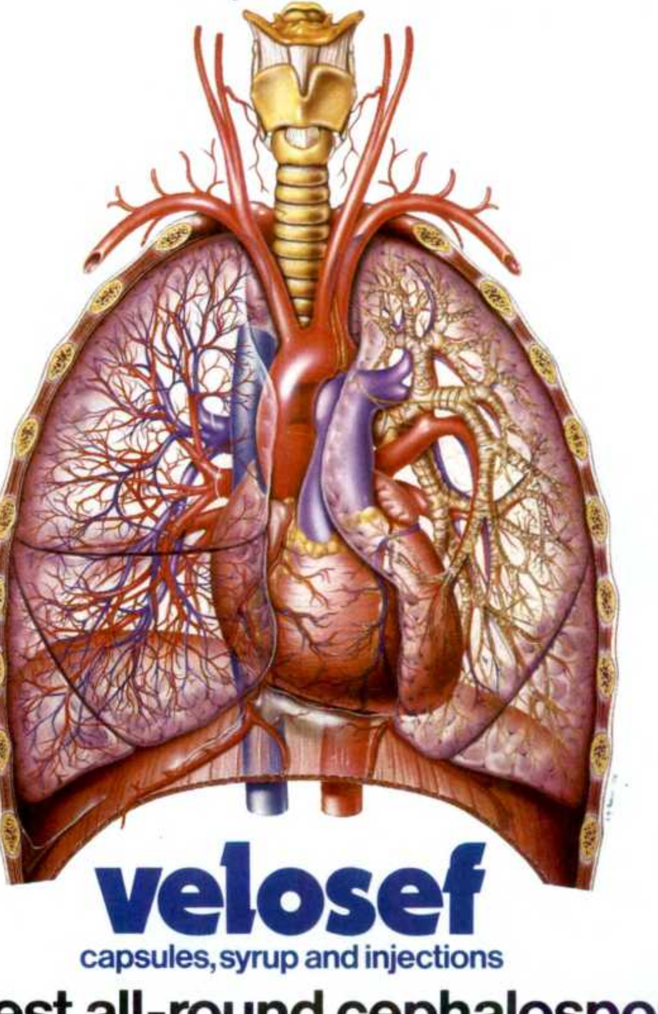

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Reference: 1) Scot. Med. J 1976:**21**, 210–217. Further information on Velosef (Trade Mark) is available from: Technical Services Department, E.R. Squibb & Sons Limited, Squibb House, 141–149, Staines Road, Hounslow, Middlesex. TW3 3JA. Telephone: 01-572 7422

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Coronary artery narrowing without irreversible myocardial damage or development of collaterals

Assessment of "critical" stenosis in a human model

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SUMMARY Postinfarction cardiac rupture is the result of thrombotic occlusion of a functional end artery with no previous myocardial damage in the perfusion area of the occluded artery. The pre-existing atherosclerotic stenosis at the site of thrombosis is thus "non-critical" in relation to the development of collateral vessels and/or irreversible myocardial damage.

Eleven cases of postinfarction cardiac rupture were studie by microscopy of cross-sections of the thrombosed segments. At the site of the thrombosis, pre-existing atherosclerosis had narrowed the lumen to 11% or less of its normal cross-sectional area. Maximal pre-existing narrowing of the proximal left anterior descending artery was found in a case with 97% stenosis (histologically measured cross-sectional area reduction) and an estimated residual lumen of 0·71 mm^2. The prestenotic luminal area which is usually considered angiographically as "normal" was in all cases shown histologically to be severely narrowed by a diffuse intimal thickening.

It is concluded that organic coronary stenosis must be far greater than 75% to be responsible for the development of collateral vessels and/or irreversible myocardial damage.

Coronary artery stenosis that limits blood flow below basal demands is usually considered critical. In human disease, however, the term "critical stenosis" is poorly defined, especially as no consistent relation has been documented between symptoms of ischaemic heart disease and the extent and severity of coronary narrowing.[1–3] In addition, a severe stenotic lesion may be bypassed and adequately compensated by collateral vessels, which make evaluation of the ischaemic significance of the stenosis, *per se*, impossible. In animal studies, however, a critical level of stenosis has been identified. Isolated proximal coronary stenosis has to reduce the luminal cross-sectional area by about 95% before resting myocardial flow fails to meet the demand.[4 5] At that degree of acute obstruction, the peripheral vascular bed is maximally dilated and further narrowing will cause myocardial ischaemia at rest.

At necropsy we are occasionally provided with a human model which is comparable with the experimental, isolated coronary stenosis. Thus it has previously been shown that a uniform patho-anatomical substrate exists in postinfarction cardiac rupture, consisting of an acute coronary occlusion with a recent myocardial infarct which is transmural and totally unprotected by scar or collateral vessels.[6] Consequently, in these hearts we find acute occlusions of functional end arteries, and the pre-existing organic stenosis at the site of thrombosis can thus be considered "non-critical" in relation to the development of collateral vessels and/or irreversible myocardial damage.

This paper presents a quantitative assessment of the pre-existing luminal narrowing in acutely thrombosed coronary arteries from 11 patients with postinfarction cardiac rupture.

Subjects and methods

Nine consecutive necropsy patients with heart rupture from Randers Hospital and two cases referred from another hospital in the same period (1 February 1980 to 30 June 1981) form the basis for this study.

After the heart was weighed the coronary arteries were gently flushed via the aorta with 100 ml 4% formaldehyde solution and then a barium gelatine

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medium at 40°C was injected under a pressure of 150 mmHg maintained for 15 minutes. The medium was hardened by cooling and angiograms were taken in different projections. The heart was fixed for two weeks in a 4% formaldehyde solution, decalcified for three weeks in EDTA (ethylenediaminetetraacetic acid), and then stored for at least one week in formalin. The main coronary arteries and those of their branches thicker than 1 mm were cross-sectioned at 3 mm intervals. Each segment, angiographically shown to be stenosed or occluded, was processed for microscopy. All thrombosed segments were cross-sectioned at 200 μm intervals and the point of maximal luminal reduction resulting from old atherosclerotic plaques was identified. The ventricular portion of the heart was cut into 1 cm thick slices parallel to the atrioventricular groove, photographed, and *x*-rayed, with each slice placed directly on the film. Several histological sections were prepared from the perfusion area of each coronary artery and from the myocardium adjacent to the rupture.

TISSUE SHRINKAGE

To calculate the shrinkage that occurs when an artery is processed for microscopy the following experiment was performed. Unfixed segments of injected arteries were dissected free from the hearts, placed directly on radiographic film, and *x*-rayed. *X*-rays were repeated after fixation, dehydration, clearing, and embedding in paraffin. During this procedure and at the final microscopical examination of the histological sections it was observed that the shrinkage of the radio-opaque medium was equal to or a little more pronounced than the shrinkage of the artery lumen. The segments where the shrinkage of the *x*-ray medium equalled the luminal shrinkage were selected for measurements. The luminal diameters were measured on the radiographs and the luminal area shrinkage resulting from tissue processing was calculated. One-hundred and fifty measurements were done on 15 different vascular segments.

Table 1 *Clinical data in 11 patients with postinfarction cardiac rupture*

Case No.	*Age (y)*	*Sex*	*Survival* (d)*	*Preinfarction cardiac symptoms†*
1	82	F	1	None
2	69	M	<1	Unstable angina
3	69	M	3	None
4	80	M	<1	None
5	71	F	<1	Unstable angina?
6	77	M	5	None
7	79	M	<1	Unstable angina
8	67	M	4 weeks	None
9	74	F	10 weeks	Unstable angina
10	86	M	<1	None
11	68	M	<1	None

*Histological dating of the infarcts according to the criteria of Mallory *et al.*[9]
†No patient had stable angina pectoris.

Table 2 *Histological and angiographic data in 11 patients with postinfarction cardiac rupture*

Case No	*Heart weight (g)*	*Thrombosed artery*	*Size of perfusion area*	*Measured histological areas*			*Calculated stenoses*		*True residual** lumen (mm²)*
				Residual lumen (mm²)*	*Original† lumen (mm²)*	*Prestenotic‡ lumen (mm²)*	*Angiographic§*	*Histological¶*	
1	430	LAD (prox.)	39%	0·47	17·28	7·56	94%	97%	0·71
2	450	LAD (prox.)	42%	1·30	15·08	7·29	82%	91%	1·95
3	370	LM	15%	0·94	11·20	2·54	63%	92%	1·41
4	490	LAD	20%	1·07	13·66	4·01	73%	92%	1·61
5	500	LAD	21%	0·26	11·33	5·51	95%	98%	0·39
6	450	R	37%	0·47	12·53	6·36	93%	96%	0·71
7	350	LAD	22%	1·47	13·78	4·32	66%	89%	2·21
8	600	LAD (prox.)	43%	0·51	24·62	5·18	90%	98%	0·77
9	440	R	37%	1·13	19·60	7·29	84%	94%	1·70
10	385	LAD	22%	0·55	13·17	4·12	87%	96%	0·83
11	430	LAD	22%	1·63	15·87	11·92	86%	90%	2·45

Abbreviations: LAD, left anterior descending artery; (prox.) indicates that the occlusion is located proximal to the first diagonal branch; LM; left marginal branch; R, right coronary artery.
* Cross-sectional luminal area at maximal stenosis resulting from old atherosclerotic plaques.
† Cross-sectional area encircled by the internal elastic membrane.
‡ Cross-sectional luminal area of adjacent prestenotic segment which, angiographically, would be judged as "normal".
§ Residual lumen/prestenotic lumen.
¶ Residual lumen/original lumen.
** Residual lumen corrected for shrinkage caused by processing for microscopy (residual lumen×3/2).

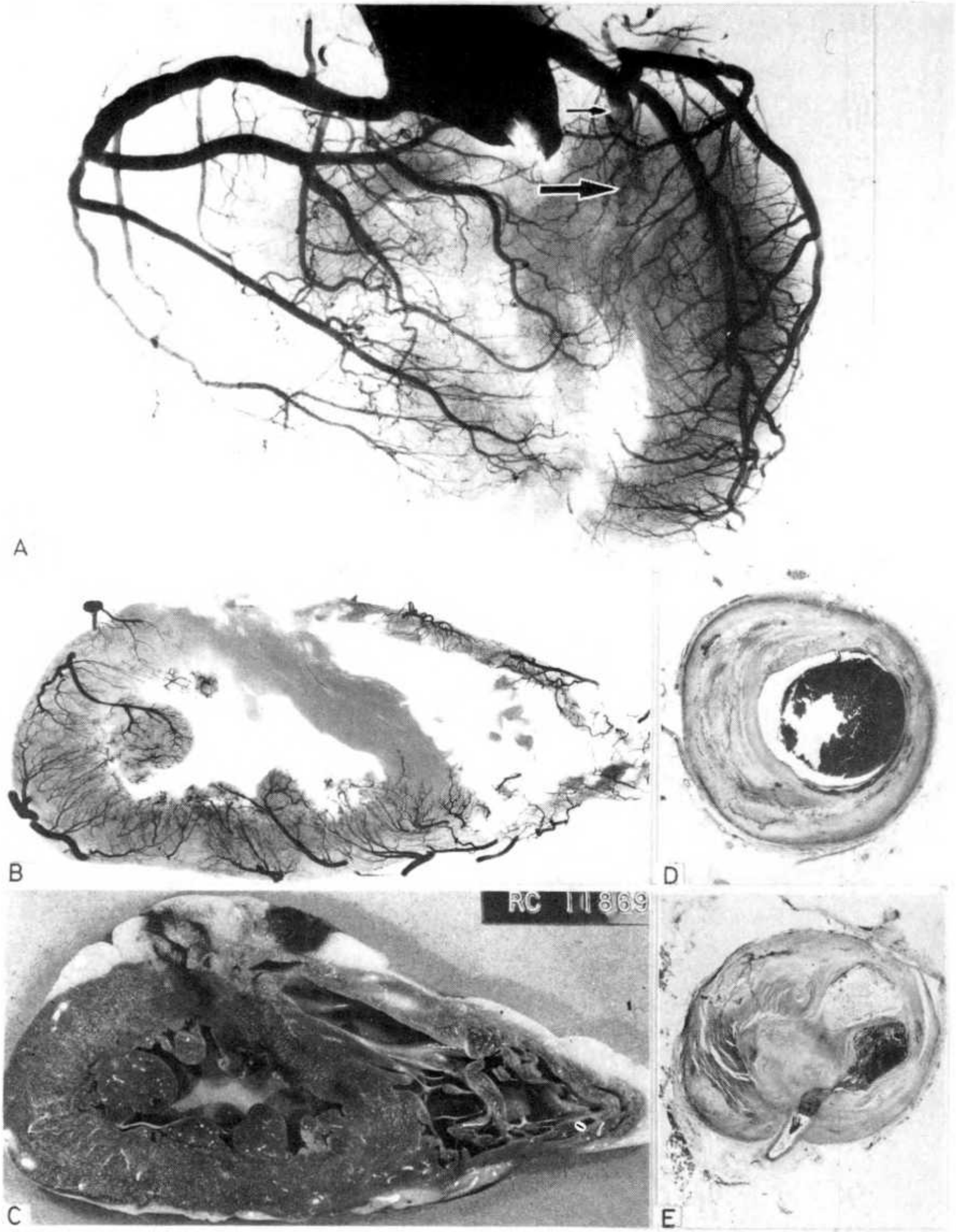

Fig. 1 *Case 2 illustrating how severe a stenosis can be without collatral development or evidence of irreversible myocardial damage in the form of scar. (A) Postmortem angiogram in the anteroposterior view showing total occlusion of the proximal left anterior descending artery (thick arrow) without collateral distal filling of the vessel (original natural size). (B) Radiograph of a transverse myocardial slice showing no collateral vascular filling in the perfusion area of the left anterior descending artery (original natural size). (C) Photograph of the same myocardial slice showing rupture of the anterior left ventricular wall. Microscopy showed anteroseptal infarction less than 1 day old; no myocardial fibrosis was present (original natural size). (D) Histological section from angiographic "normal" segment (thin arrow in A) showing diffuse intimal thickening with the lumen 64% obliterated (original magnification × 8). (E) Histological section showing occluding thrombus at the site of maximal atherosclerotic narrowing (thick arrow in A). This degree of old stenosis (91% cross-sectional area reduction) has not caused collateral development or produced irreversible myocardial damage in the form of fibrosis. In this case a histological area stenosis of 91% corresponds to an angiographic area stenosis of 82% (original magnification × 8).*

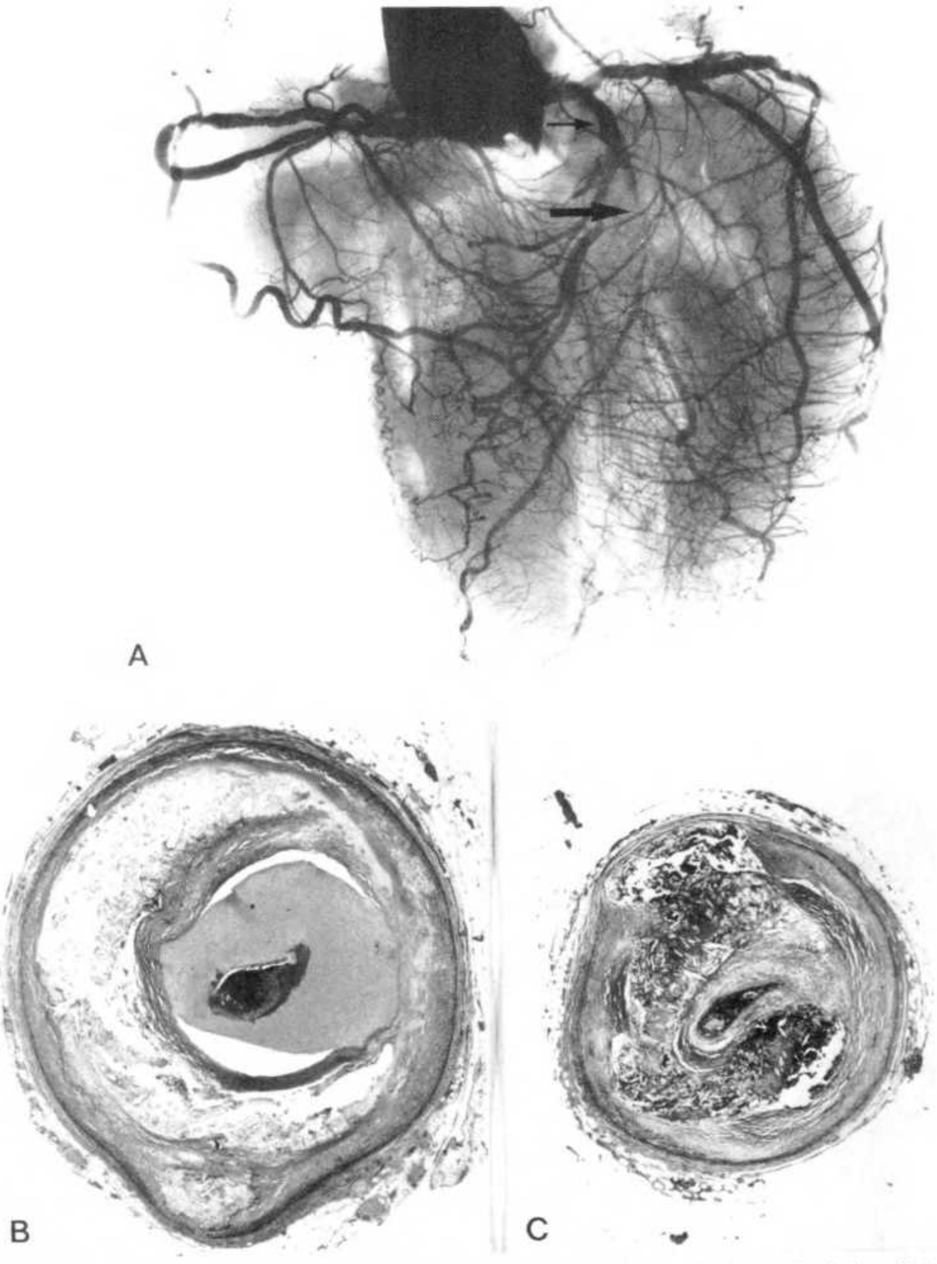

Fig. 2 *Correlation of angiographic and pathological findings (case 5). (A) Angiogram showing total occlusion of left anterior descending artery (thick arrow) with poor collateral distal filling of the vessel (original natural size). (B) Histological section of the left anterior descending artery just after the bifurcation of the left main artery (thin arrow) where the vessel angiographically appears "normal" with a wide lumen. Nevertheless, the luminal narrowing resulting from diffuse atherosclerotic intimal thickening is 71% at that point. That is the reason why the real stenosis is consistently underestimated angiographically (original magnification × 14). (C) Histological section from the left anterior descending artery at the site of maximal stenosis resulting from old atherosclerotic plaques (thick arrow); the residual lumen is occluded by a recent thrombus. The histological area stenosis of 98% corresponds in this case to an angiographic area stenosis of 95% (original magnification × 14).*

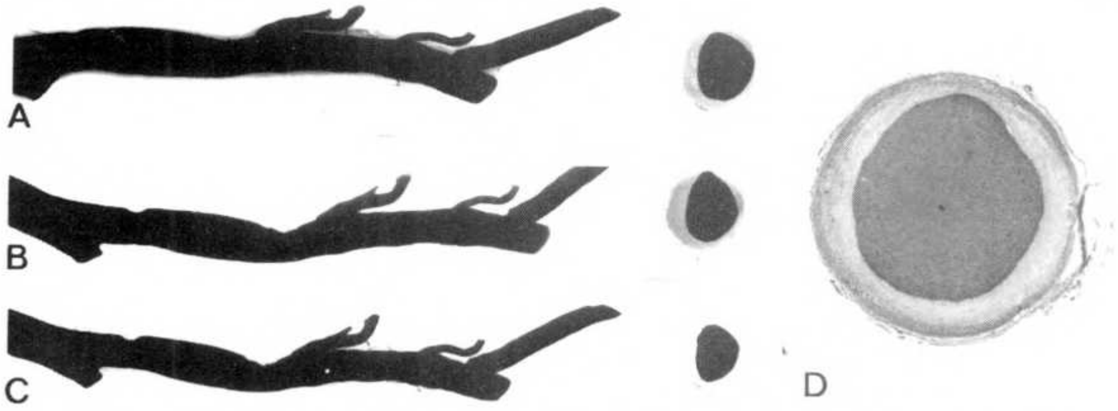

Fig. 3 *Shrinkage of tissue and contrast medium caused by processing for microscopy. (A) Radiograph of an unfixed vascular segment placed directly on the x-ray film. (B) The same segment after fixation and decalcification. (C) The same segment after dehydration, clearing, and paraffin infiltration. That the shrinkage of the contrast medium equals the luminal shrinkage is shown by radiographs of corresponding cross-sections and by microscopy of the final histological sections (D). The total shrinkage (A to C) results in a reduction of the luminal area to approximate two thirds of the original area of the unprocessed vessel. ((A), (B), and (C) original magnification × 2·5; (D) original magnification × 11)).*

PERFUSION AREA

The relative amount of ventricular myocardium supplied by the three large coronary arteries varies according to the anatomy of the coronary artery tree. The perfusion areas of the coronary arteries were identified from the angiograms, and the percentage of ventricular myocardium supplied by each artery was determined according to the results of Kalbfleisch and Hort.[7] The perfusion area of the first diagonal branch was considered as large as that of the left anterior descending artery distal to the first diagonal branch.[8]

DEFINITIONS

Histological stenosis: the ratio between the cross-sectional area of the residual lumen and the assumed original cross-sectional luminal area of the vessel at the point under consideration (the area encircled by the internal elastic membrane). All cross-sectional areas are calculated from measurements of maximal and minimal diameters assuming an elliptical cross-section (measured by projection microscopy using a Reichert Lanometer).

Angiographic stenosis: the ratio between the stenotic luminal area and the greatest prestenotic luminal area (which angiographically would be judged as "normal"). As the vessels in question are thrombosed and thus not visualised on the angiograms, the two areas had to be determined by microscopy of the histological sections.

Results

Clinical and pathological findings are summarised in Table 1 and 2.

Recent thrombi superimposed on atherosclerotic plaques were found in all patients, and the site of myocardial rupture corresponded with the point of arterial occlusion. At the site of the thrombus, all patients had histological stenosis of more than 89% caused by old atherosclerotic plaques. Apart from cases 8 and 9, the angiograms disclosed no collateral vessels bypassing the thrombotic occlusions (Fig. 1 and 2) and careful microscopical examination of the myocardium showed no fibrosis in the perfusion area of the thrombosed artery. Cases 8 and 9 had ruptured ventricular aneurysms. The prestenotic segments which, on angiograms, are usually considered as "normal" were in all cases severely narrowed because of diffuse intimal thickening (confluent atherosclerotic lesions) (Fig. 1 and 2). Formalin fixation did not cause any significant tissue shrinkage (no difference between vessels dissected free and vessels in situ) but the subsequent tissue processing resulted in a reduction of the luminal area to approximate two-thirds of the original area of the unfixed vessel (median: 65%, range: 50% to 74%) (Fig. 3).

Discussion

Necropsy studies have shown that the infarction size is usually smaller than the perfusion area of the obstructed vessel[10-12] and even cases of total coronary occlusion with no myocardial damage have been reported.[11 13] The ability of collateral vessels to protect jeopardised myocardium is thus obvious. Therefore, to evaluate the ischaemic significance of organic stenoses, one has to identify stenotic lesions not bypassed by collateral vessels. But as many functional collateral vessels are below the resolution of modern cineangiographic equipment,[14] in vivo determination of the human "critical stenosis" may be unreliable. The degree of coronary artery narrowing causing irreversible myocardial damage is thus poorly defined clinically. In fatal heart disease, however, the necropsy occasionally discloses postinfarction cardiac rupture, and in these cases the existence of significant collateral vessels can be excluded in the light of functional considerations, not merely because of inability to detect such vessels angiographically.

Thus, using a refined injection and dissection technique, Wessler *et al.*[6] have shown that postinfarction cardiac rupture is the result of thrombotic occlusion of a functional end artery with no evidence of previous myocardial damage (fibrosis) in the perfusion area of the thrombosed artery. The reliability of their technique in showing collateral vessels in human hearts without coronary artery disease has been questioned[15 16] but their method has been reliable in hearts with coronary occlusions.[15] The present study was not undertaken to clear up the pathogenesis of postinfarction cardiac rupture, but our results are in agreement with the results of Wessler *et al.* Cases 8 and 9 are unusual cases of late myocardial rupture (ruptured aneurysms four and 10 weeks after the acute infarction) and the angiographically visible collateral vessels have probably developed secondarily to the thrombotic occlusions.

The aim of our study was to determine the maximal degree of old organic obstruction in the thrombosed coronary artery in cases of postinfarction cardiac rupture. These stenoses have not yet reached a degree that causes collateral development and/or irreversible myocardial damage.

Many pathologists consider an histological area stenosis of 75% as significant.[1 17 18] This study, however, shows that a pure organic stenosis far greater than 75% may be well tolerated. Thus, stenoses greater than 95% were observed without evidence of irreversible myocardial damage in the corresponding perfusion area.

Minor degrees of organic obstruction may of course be clinically significant in causing myocardial ischaemia and angina during exercise and, if vasoconstriction (spasm) is superimposed, even at rest.[19 20]

Histological stenosis is not comparable with angiographic stenosis. The pathologist compares the residual lumen with the presumed original lumen (area encircled by the internal elastic membrane) while the clinician compares the most narrowed segment with the adjacent "normal" arterial segment as depicted on the angiogram. The adjacent "normal" segment, however, is never normal, as the coronary arteries in ischaemic heart disease in addition to focal stenotic lesions have diffuse intimal thickening[18] which often corresponds to a histological area reduction of 75%.[1 18] The result is that the angiographer compares stenotic segment with adjacent "normal looking" but, nevertheless, narrowed segment, and the real degree of stenosis is thus consistently underestimated. To overcome this problem in angiographic-histological correlative studies, it is necessary to measure the stenotic residual lumen precisely and then to calculate the true size of the lumen. The clinician has to compensate for dimensional errors caused by angiographic magnification while the pathologist has to correct for postmortem alterations and tissue shrinkage secondary to processing for microscopy. Our histological procedures resulted in an area reduction to two-thirds of the area of the unprocessed vessel. This figure is in general agreement with the results obtained by measurements of volume changes of whole organs and tissue specimens fixed in formalin and processed for embedding in paraffin.[21 22]

McMahon *et al.*[23] have measured angiographically the minimum cross-sectional lumen area in patients with unstable angina and proximal single vessel disease without collateral vessels and found it 0·6 mm² (92% cross-sectional area reduction). Our cases 1, 6, and 8 show proximal stenoses with a residual lumen of the same magnitude (0·71, 0·71, and 0·77 mm²). As all stenoses in our cases are "non-critical", the present study fully confirms the observation of McMahon *et al.* that a very severe coronary stenosis can be tolerated in a functional end artery without irreversible myocardial damage in the perfusion area of the obstructed vessel. Stenotic coronary lesions with less than 90% angiographic *diameter* reduction can undoubtedly produce myocardial ischaemia and anginal pain during exercise, but from a haemodynamic point of view they are of moderate degree only, since they are practically never accompanied by angiographically visible collateral circulation.[14 24] The present pathological study confirms clinical observations that an organic stenosis has to be very severe to be held responsible for development of collateral vessels.

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Captopril as treatment for patients with pulmonary hypertension

Problem of variability in assessing chronic drug treatment

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SUMMARY We gave captopril, an angiotensin converting-enzyme inhibitor, to four patients with unexplained pulmonary hypertension to see if it would lower pulmonary arterial pressure or pulmonary vascular resistance. The patients were studied at rest and during supine bicycle exercise, before and after 48 hours of captopril treatment (up to 450 mg/day). During the treatment, each patient was monitored, with systemic and pulmonary pressures measured hourly, and cardiac output every two to four hours. We found no significant effect of captopril, either at rest or with exercise, on the cardiac output, pulmonary artery pressure, or pulmonary vascular resistance, measured at the end of 48 hours treatment. We noted, however, that during the 48 hour period, all patients showed pronounced swings in their pulmonary and systemic artery pressures and cardiac outputs that had no relation to the administration of captopril or time of day. We conclude that captopril appears to be ineffective in causing a sustained reduction in the pulmonary artery pressure or pulmonary vascular resistance in patients with primary pulmonary hypertension. It appears, however, that these patients experience spontaneous variability in their pulmonary resistance from hour to hour which needs to be further studied before a reliable assessment of long-term drug treatment can be made.

Primary pulmonary hypertension is regarded as a fatal disease for which no established treatment exists.[1] There has been recent interest in the use of vasodilator drugs in these patients in the hope of lowering their pulmonary arterial pressures and pulmonary vascular resistances.[2] Several case reports have described the beneficial effects of such drugs,[3-5] but no single agent has been identified that is clearly superior in this regard.[6]

Captopril represents a new class of vasodilator drugs, the angiotensin converting-enzyme inhibitors. The role that angiotensin II plays in the development of pulmonary hypertension is unclear, but it has been suggested that it may be a factor in some types of pulmonary hypertension.[7] The peptidyl dipeptide hydrolase that converts angiotensin I to angiotensin II is found largely in the lung,[7] raising the possibility that the drug may be able to work locally to reduce pulmonary artery pressure.

In this study we tested the hypothesis that captopril would lower the pulmonary artery pressure and pulmonary vascular resistance in patients with vasoconstrictive pulmonary hypertension either at rest or with exercise. In addition, we made additional observations regarding the variability in the haemodynamics of the pulmonary and systemic vasculature in these patients by continuously monitoring their pulmonary pressures and cardiac outputs for 48 hours during the initiation of drug treatment.

Subjects and methods

PATIENT SELECTION

The study group consisted of four patients with pulmonary hypertension of undetermined aetiology. Each patient had a chest *x*-ray film, full pulmonary function tests, and lung scanning to exclude interstitial lung disease or pulmonary emboli. They also had echocardiography and a full right and left heart catheterisation to exclude cardiac causes for pulmonary hypertension, including left to right shunts. In addition, three patients had open lung biopsies which

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were consistent with primary or "idiopathic" pulmonary hypertension, without evidence for any occult pulmonary disease (see Table 1). A definite diagnosis was made of primary pulmonary hypertension in three patients. The fourth patient (case 2) had an antecedent history of closure of a ventricular septal defect at 3 years of age. Though he had no residual shunt, it is possible that he represents persistent pulmonary hypertension, rather than primary pulmonary hypertension.

PROCEDURE

The study was approved by the Institutional Review Committee and informed consent was obtained from each patient. All patients had been previously given a vasodilator drug (tolazoline and/or hydralazine) intravenously, with a resultant fall in their pulmonary vascular resistances (mean reduction 20%, range 3% to 47%) (see Table 1). Patients were rested in bed for at least 12 hours before the study, on a general unrestricted salt diet, and no change was made in their drugs. Control haemodynamic measurements were obtained, after an overnight fast, in the cardiac catheterisation laboratory. After the resting data were obtained, the patients were exercised on a supine bicycle ergometer for four minutes at 350 kpm. They were then transferred, with arterial and Swan-Ganz catheters in place, to the coronary care unit where they underwent continuous monitoring until the morning of the third day (40 to 46 hours later) while captopril was given orally every eight hours in the following doses: 25 mg, 50 mg, 100 mg, 150 mg. The patients were kept on the highest dose of captopril tolerated (which was 150 mg every eight hours except for case 3 who was kept on 100 mg every eight hours because of systemic hypotension). The patients returned to the catheterisation laboratory on the morning of the third day, after an overnight fast, 90 minutes after their last dose of captopril. Haemodynamic measurements were again taken with the patient at rest, and then with exercise, which ended the study.

HAEMODYNAMIC STUDY

Either a 7F Swan-Ganz catheter or a 7F Cournand catheter was placed in the pulmonary artery via an antecubital vein cutdown. The radial artery was cannulated with a short Teflon catheter. Measurements were made of the systemic arterial pressure (SAP), right atrial pressure (RAP), pulmonary artery pressure (PAP), and pulmonary wedge pressure (PWP) (in mmHg) with a 23db Gould-Statham pressure transducer and recorded on a multichannel recorder (E for M, VR 16). Mean pressures were derived from electronic integration. Thermodilution cardiac outputs (CO) were determined (in litres/min) using standard techniques (Edwards 9150 CO computer). Fick cardiac outputs were performed with exhaled gas analysed in a paramagnetic oxygen analyser (Beckman MMC), and arterial oxygen saturations measured in a co-oximeter (IL Instrument Laboratory 282). Values for vascular resistances were calculated (in dynes s cm^{-5}) from the following formulae:

Systemic vascular resistance $(SVR) = (SAP - RAP/CO) \times 80$

Total systemic resistance $(TSR) = (SAP/CO) \times 80$

Pulmonary vascular resistance $(PVR) = (PAP - PWP/CO) \times 80$

Total pulmonary resistance $(TPR) = (PAP/CO) \times 80$

Exercise was performed in the supine position with a bicycle ergometer at 350 kpm for four minutes, with pressures recorded for the last 10 seconds of each minute of exercise and cardiac output measured during the fourth minute of exercise. One patient showing a favourable drug effect was placed on long-term oral treatment with repeat catheterisation after three months.

STATISTICAL ANALYSIS

Mean levels of the haemodynamic variables, before and after administration of captopril, were calculated for the resting and exercise states. Because of the small number of the sample size a simple non-parametric test (the sign test) was selected to assess

Table 1 *Characteristics of patients studied*

Case No.	*Age/Sex*	*Known length of time with pulmonary hypertension*	*Findings on lung biopsy*	*Other drugs*	*Response to vasodilator*
1	21 F	2 y	Severe medial hypertrophy, mild intimal proliferation H and E grade 3	None	PVR down 10% with TOL
2	21 M	10 mth	Medial hypertrophy, distinct intimal fibrosis H and E grades 3–4	None	PVR down 20% with TOL
3	45 M	10 y	Mild medial hypertrophy and intimal proliferation H and E grades 2–3	Digoxin 0·25 mg, frusemide 40 mg	PVR down 30% with TOL and 46% with HYD
4	47 M	7 y	Not done	None	PVR down 3% with HYD

H and E, Heath and Edwards classification for pulmonary hypertension[17]; HYD, hydralazine 0·3 mg/kg intravenously; PVR, pulmonary vascular resistance; TOL, tolazoline 1 mg/kg intravenously.

the statistical significance of the drug effects on each variable. The variability of haemodynamic indices noted over time was calculated as the mean value for each individual patient, with the corresponding standard deviation from the mean.

Results

The results of the effects of captopril on haemodynamics at rest after 48 hours of treatment is shown in Table 2. As a group, the patients had mildly reduced cardiac outputs and conspicuously raised pulmonary artery pressures and pulmonary vascular resistances. With captopril treatment there was an overall mean increase in cardiac output from 3·23 to 3·54 l/min, and a reduction in pulmonary vascular resistance from 1363 to 1310 dynes s cm^{-5}. The mean pulmonary artery pressure rose from 62 to 65 mmHg, but none of these haemodynamic changes was of statistical significance. The only significant effect of the drug was in reducing the systemic vascular resistance, from 2532 to 2054 dynes s cm^{-5}.

EFFECTS OF CAPTOPRIL ON EXERCISE (Table 3)

As a group, the cardiac output was reduced from 5·42 to 5·10 l/min, and the pulmonary artery pressure was increased, from 87 to 91 mmHg with exercise on captopril. Total pulmonary resistance increased from 1393 to 1430 dynes s cm^{-5}, while total systemic resistance was virtually unchanged. None of these effects, however, achieved statistical significance.

LONG-TERM TREATMENT WITH CAPTOPRIL

The relative effect of captopril on the systemic and pulmonary resistances was also noted in each patient. In three of these patients the reduction that occurred at rest in systemic vascular resistance exceeded the reduction in pulmonary vascular resistance. In one patient, the opposite was true, namely the pulmonary resistance fell more than the systemic vascular resistance (24% vs 13%, respectively). This patient was placed on long-term oral treatment with 150 mg captopril three times a day for three months, at which time she was restudied. The results of the restudy are shown in Table 4. Though there was a further reduction in systemic vascular resistance noted after three months, we could not demonstrate any sustained reduction in pulmonary artery pressure, nor was there any apparent beneficial influence on exercise haemodynamics. In addition, the drug now appeared to have a relatively greater effect on the systemic resistance than the pulmonary resistance as compared with the control state (26% vs 13% reduction, respectively). For these reasons the drug was discontinued.

VARIABILITY OF PULMONARY ARTERY PRESSURE IN PULMONARY HYPERTENSION

Each of the patients in the study group were moni-

Table 2 *Effects of captopril on haemodynamics at rest**

Case No.	*Cardiac output (l/min)*		*Mean systemic pressure (mmHg)*		*Mean pulmonary pressure (mmHg)*		*Pulmonary wedge pressure (mmHg)*		*PVR (dynes s cm^{-5})*		*SVR (dynes s cm^{-5})*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	3·57	4·23	97	100	70	66	3	6	1501	1135	2106	1834
2	3·55	4·06	74	80	64	78	3	2	1375	1497	1662	1536
3	3·28	3·13	112	82	65	62	6	6	1439	1431	2585	1942
4	2·53	2·72	124	104	48	52	12	12	1138	1176	3776	2903
Mean	3·23	3·54	102	92	62	65	6	7	1363	1310	2532	2054
SEM	0·24	0·36	10·8	6·1	4·8	5·4	2·1	2·1	79	90	455	296
p value	NS		NS		NS		NS		NS			0·0625

PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.
*Measurements on captopril treatment were made 90 minutes after the last dose administered.

Table 3 *Effects of captopril on haemodynamics with exercise*

Case No.	*Cardiac output (l/min)*		*Mean systemic pressure (mmHg)*		*Mean pulmonary pressure (mmHg)*		*Total pulmonary resistance (dynes s cm^{-5})*		*Total systemic resistance (dynes s cm^{-5})*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	7·24	6·23	118	130	90	110	994	1412	1304	1669
2	5·49	6·20	109	103	100	100	1457	1290	1588	1329
3	5·16	4·37	112	92	94	92	1457	1684	1736	1684
4	3·80	3·60	134	124	62	60	1305	1333	2821	2755
Mean	5·42	5·10	118	112	87	91	1303	1430	1862	1859
±SEM	0·71	0·66	5·6	8·9	8·4	10·8	109	88	332	310
p value	NS		NS		NS		NS		NS	

Table 4 *Short-term and long-term effects of captopril in one patient with primary pulmonary hypertension*

	Mean systemic pressure (mmHg)	*Mean pulmonary pressure (mmHg)*	*Cardiac output (l/min)*	*Systemic vascular resistance (dynes s cm^{-5})*	*Total systemic resistance (dynes s cm^{-5})*	*Pulmonary vascular resistance (dynes s cm^{-5})*	*Total pulmonary resistance (dynes s cm^{-5})*
R	97	70	3·57	2106	2173	1501	1569
Ex	118	90	7·24		1304		994
R-Cl	100	66	4·23	1834	1981	1135	1248
Ex-Cl	130	110	6·23		1669		1412
R-C2	97	76	4·08	1552	1552	1312	1490
Ex-C2	139	132	7·08		1288		1344

Cl, with captopril after 48 hours; C2, with captopril after three months; Ex, exercise; R, rest.

tored in the coronary care unit for 40 to 46 hours after the establishment of control haemodynamics in the catheterisation laboratory while captopril was given, with pulmonary and systemic pressures recorded hourly and cardiac output measured every two to four hours. We plotted the hourly changes in pulmonary artery pressure, systemic pressure, cardiac output, total systemic resistance, and pulmonary vascular resistance that occurred over this period in each patient to determine if a beneficial effect of the drug could be related to the dose or timing of the drug administration. We noted that each patient showed pronounced swings in the level of their pulmonary and systemic pressure and cardiac output that had no relation to the time or dose given of captopril, time of day, meals, or wakefulness (see Table 5 and Fig. 1 and 2). Though the study design dictated that the short-term effects of captopril be reassessed in the catheterisation laboratory after 48 hours of treatment, it became apparent retrospectively that the timing of the final measurements could have altered the assessment of drug effectiveness.

Table 5 *Variability in pulmonary artery pressure, systemic pressure, and cardiac output over 48 hours of continuous monitoring during captopril administration*

	Case 1	*Case 2*	*Case 3*	*Case 4*
Mean pulmonary arterial pressure (mmHg)				
Minimum	46	40	64	48
Maximum	86	65	93	66
Mean (over 48 h)	68	57	76	56
±SD	10·8	5·0	4·9	6·0
Mean systemic pressure (mmHg)				
Minimum	61	50	67	98
Maximum	123	83	112	144
Mean (over 48 h)	89	69	82	118
±SD	19·0	9·5	7·4	12·2
Cardiac output (l/min)				
Minimum	3·56	2·85	3·13	2·53
Maximum	4·35	5·46	5·94	3·40
Mean (over 48 h)	4·04	4·02	4·56	2·86
±SD	0·22	0·60	0·65	0·47

Discussion

Although no established treatment for patients with primary pulmonary hypertension exists, vasodilating drugs have been used recently in these patients with the hope of achieving a sustained reduction in the pulmonary artery pressure. Reports of sustained beneficial drug effects have been sporadic and limited to only a few patients.[6] Current interest has been focused largely on drugs that are direct arterial vasodilators, such as hydralazine, diazoxide, and nifedipine. Captopril represents a unique drug in that it appears to work by its ability to block angiotensin II,[8] a potent vasconstrictor. Like the direct vaso-

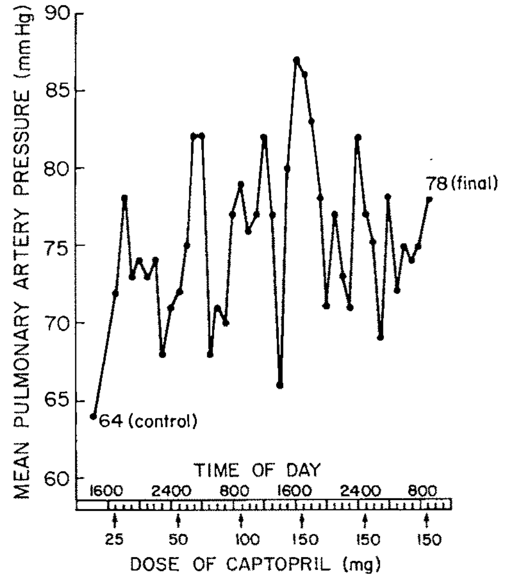

Fig. 1 *The hourly changes that occurred in the mean pulmonary artery pressure of one of the patients studied plotted over time. The timing and dosage of captopril given are indicated, as well as the time of day. There does not appear to be any relation between drug administration and the pulmonary arterial pressure recorded. Peak effect of oral captopril is 90 minutes.*

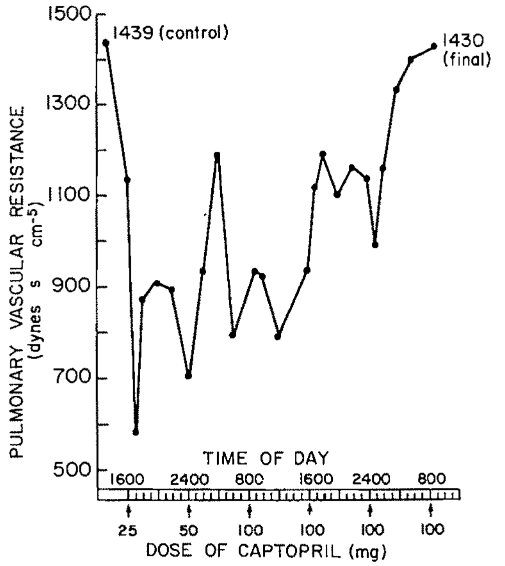

Fig. 2 *The serial changes in the calculated pulmonary vascular resistance in another patient plotted over time. The timing and dosage of captopril given are indicated, as well as the time of day. There does not appear to be any relation between the drug administration and the pulmonary vascular resistance. Variability in the pulmonary pressure and pulmonary resistance was noted in all of the patients studied.*

dilators, captopril has been shown to be effective in lowering the systemic arterial pressure in patients with essential hypertension,[9] and in raising the cardiac output in patients with heart failure.[10]

Our study failed to show any sustained beneficial effect of captopril on the pulmonary haemodynamics of patients with primary pulmonary hypertension. Though the role of angiotensin II in the genesis of pulmonary hypertension is unclear,[11] captopril offered the possibility of reducing the pulmonary artery pressure either through angiotensin II blockade, or by increasing circulating prostaglandin E1, a potent pulmonary vasodilator.[12] Though neither renin nor prostaglandin E1 levels were measured in this study, the drug did have the expected pharmacological effect of reducing the systemic vascular resistance in every patient.

One may question whether captopril would have been effective if larger doses were administered. The decision to limit the maximum daily dose to 450 mg was based on data showing that higher doses have been no more effective in lowering the systemic blood pressure in patients with essential hypertension, but are associated with an increased incidence of untoward effects.[13] Captopril has been effective in lowering systemic pressures in patients with severe hypertension resistant to treatment in doses of 150 mg or less every eight hours.[14]

It is also possible that captopril would have been effective if it were administered long term. There are some data to suggest that the beneficial effects that captopril has in raising the cardiac output in patients with heart failure are enhanced the longer the drug is administered.[15] In the single patient who had the most favourable response to short-term captopril, we were unable to show any improvement when the drug was continued for three months.

The variability in pulmonary and systemic pressures and cardiac output that was noted during the period of continuous monitoring uncovers an aspect of primary pulmonary hypertension that needs to be addressed. It has never been determined what constitutes a clinically significant reduction in pulmonary arterial pressure in these patients. Variability in the pulmonary arterial pressure of one other patient with primary pulmonary hypertension has been previously described,[16] but this was felt to be an unusual occurrence. Our experience suggests that this may be a common phenomenon. In order to establish what magnitude of change in pulmonary artery pressure or pulmonary vascular resistance would be significant, the amount of spontaneous alteration of these variables that occurs in these patients needs to be known. All of the patients in our study were receiving captopril while being monitored. Thus it is possible that the variability noted was drug related. We were unable, however, to associate the hourly changes in pulmonary or systemic resistance with the dosage or time of drug administration, time of day, meals, or wakefulness. It remains to be determined how much variability exists in the pulmonary and systemic circulations of these patients when no drugs are being taken.

In summary, captopril appears to be ineffective in producing a sustained reduction in pulmonary arterial pressure or pulmonary vascular resistance in patients with primary pulmonary hypertension, at rest or with exercise. Such patients, however, show a distinct spontaneous variability in their systemic and pulmonary pressures and cardiac outputs from hour to hour. Thus, in order to establish what change in pulmonary arterial pressure or pulmonary vascular resistance would be significant with long-term oral drug treatment in an individual patient, a prospective study to assess the magnitude of this variability in these patients when untreated is needed.

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Left ventricular function in hypothyroidism
Responses to exercise and beta adrenoceptor blockade

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SUMMARY The effects of exercise and beta adrenoceptor blockade on left ventricular function were assessed in eight patients with hypothyroidism before and during thyroxine replacement treatment. Left ventricular ejection fraction, measured by radionuclide ventriculography, was reduced in hypothyroid patients at rest and on exercise. The rise in ejection fraction with exercise was, however, similar in both groups. Pretreatment with intravenous propranolol reduced the ejection fraction at rest 9% in both hypothyroid and euthyroid patients and reduced the rise on exercise. Directional changes in a second index of myocardial contractility based on the shape of the ventricular volume curve paralleled the changes in the ejection fraction. Left ventricular function is therefore reversibly depressed by thyroid hormone deficiency but responses to exercise and beta adrenoceptor blockade are normal. There is no evidence of altered adrenergic sensitivity in the control of myocardial contractility in hypothyroidism.

The clinical effects of varying thyroid function on the cardiovascular system have been recognised for many years. The mechanism of altered myocardial contractile function in hypothyroidism has, however, been less intensively studied. The bradycardia and cardiomegaly of myxoedema are familiar, and experimentally impaired myocardial contractility is well documented.[1-3] A few studies in man, mainly using measurement of systolic time intervals, have confirmed impaired myocardial contractile function by showing prolongation of the pre-ejection period[4-6] though changes in left ventricular ejection time have been inconsistent.[4 6 7] More recently, echocardiographic techniques have been used to show the relation between thyroid hormone levels and velocity of circumferential fibre shortening at all levels of thyroid function.[8]

The influence of the sympathetic nervous system in maintaining myocardial contractile function in states of thyroid hormone deficiency is unknown. Early studies suggested that alterations in cardiac sensitivity to catecholamines could not explain the hypodynamic circulatory state characteristic of the condition.[9 10] Radioligand binding studies, however, have shown that both beta and alpha adrenoceptor density is decreased in ventricles from propylthiouracil-treated rats,[11] thus providing a mechanism for reduced adrenergic sensitivity. Myocardial cyclic AMP and contractile responses to beta adrenoceptor agonists were not assessed and therefore the functional significance of these observations remains uncertain.

The purpose of this study was to examine left ventricular contractile function and its response to exercise and beta adrenoceptor blockade in patients with hypothyroidism before and after thyroxine replacement treatment. In the absence of major changes in preload and afterload, left ventricular ejection fraction reflects the intrinsic contractile state of the heart. Radionuclide ventriculography is a sensitive and non-invasive technique for assessment of ventricular function at rest and on exercise.

Patients and methods

Eight hypothyroid patients, all women, with a mean age of 53 years (range 37 to 69 years) were investigated. The diagnosis of hypothyroidism was made clinically and on the basis of reduced levels of plasma total thyroxine (T_4) associated with a rise in plasma thyrotrophin (TSH) (Table 1). No patients were receiving drugs at the time of the first investigation. Seven had spontaneous primary hypothyroidism and one (case 8) developed hypothyroidism after 15 mCi radioiodine ^{131}I for hyperthyroidism four months

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Table 1 *Age at presentation, weight, and thyroid function at time of angiographic investigation in patients when hypothyroid and euthyroid*

Hypothyroid					*Euthyroid*				
Case No.	*Age (y)*	*Wt (kg)*	*Plasma total T_4 (nmol/l)*	*Plasma TSH (mU/l)*	*Wt (kg)*	*Plasma total T_4 (nmol/l)*	*Plasma TSH (mU/l)*	*T_4 replacement dose (mg/d)*	*Interval between 1st and 2nd study (mth)*
1	46	55·0	<20	>85·0	50·9	88	3·9	0·15	5
2	57	65·0	35	51·7	61·5	116	3·9	0·15	8
3	59	125·0	<20	>85·0	105·0	120	3·6	0·15	8
4	37	81·0	28	63·5	80·0	78	3·8	0·10	5
5	59	69·6	26	74·0	64·7	90	3·0	0·15	4
6	50	67·4	<20	64·0	64·8	79	2·3	0·10	6
7	69	74·5	24	>81·0	75·8	83	2·6	0·15	4
8	44	49·6	<20	36·3	48·6	114	1·7	0·10	5

previously. One patient (case 2) gave a history of mild chest pain on exertion compatible with angina pectoris but specific cardiac symptoms were absent in the remainder. All gave informed consent to the investigations that were approved by our local ethical committee. All patients were clinically free from heart failure at the time of study. Cardiomegaly (cardiothoracic ratio 55%) was noted on routine chest radiograph in case 7. Seven of the eight patients showed non-specific ST/T wave changes on the resting electrocardiogram.

Each patient was restudied between four and eight months after thyroxine replacement treatment when clinically and biochemically euthyroid. Details of thyroxine treatment and thyroid function tests when euthyroid are shown in Table 1. Patients had been biochemically euthyroid for at least four weeks before restudy. Case 2 showed an increase in the frequency of exertional chest pain in the first six weeks after starting thyroxine and for this reason thyroxine replacement was increased gradually over six months and combined with propanolol and long acting nitrates. Both of these drugs were discontinued in this patient four weeks before repeat study without change in symptomatology.

Isotope ventriculograms were performed in the supine position with cardiac imaging in the 30° left anterior oblique projection using a Nuclear Enterprises Mk 5HR gamma camera. After an intravenous bolus injection of 15 mCi ^{99m} technetium electrolytically labelled human serum albumin,[12] precordial counts were transferred and stored in 20 ms frame format in a PDP 11/34 computer (Digital Equipment Corporation). The accumulation was triggered by the R wave of the patient's electrocardiogram, recorded from chest lead V5, each frame being updated by successive cardiac cycles until 300 to 500 beats had been accumulated. At the end of the accumulation period, the frames were displayed in rapid sequence or movie format on a screen. The ventricular outline was selected from the display using a joy-stick and data from within this outline displayed to produce the uncorrected ventricular volume curve. The ventricular region displayed could be checked and where necessary altered by displaying the volume curves from individual pixels. Background subtraction was made from a crescentic shell of the lateral and inferior ventricular border corrected to provide an area equal to the left ventricle and the left ventricular ejection fraction was calculated from this corrected time activity curve.[13] A further index of ventricular function was calculated as the mean ejection time, (Ts) expressed as a proportion of ventricular ejection time. Ts was defined by

$$\frac{\sum_i (V_i - V_{i+1}).\frac{(t_i + t_{i+1})}{2}}{\sum_i (V_i - V_{i+1})}$$

where V_i is the relative volume at time t_i during systole. Ts was therefore derived from the sum of the products of successive volume changes and the average time between these frames. Left ventricular ejection time (LVET) was taken to be the time during which 98% of the total volume change in systole took place. The Ts: LVET ratio thus measures the shape of the volume curve in systole[14]; if a greater proportion of the volume empties in early systole then the ratio will be reduced. Regional myocardial fibre shortening is maximal during early systole and the ratio will thus correlate inversely with the intrinsic contractile state of the heart.

Patients rested for 15 minutes before the start of each study. Ventricular volume curves were constructed over 500 beats at rest and over 300 to 500 beats during supine exercise on a bicycle ergometer. The work rate was adjusted for each patient between 300 and 600 kpm/min and exercise continued for a further two to three minutes before initiating data accumulation. After a further 30 minute rest period, propranolol 0·15 mg/kg (ICI Pharmaceuticals, UK) was given over five minutes by intravenous injection and the procedure repeated after 15 minutes. Systolic blood pressure was measured by the same observer using a mercury sphygmomanometer at rest and on exercise before and after propranolol. The same procedure at the same work loads was used for each patient at restudy when euthyroid.

Thyroid function tests were undertaken before each study. Plasma total T_4 was measured by specific radioimmunoassay.[15] The interassay precision level using anonymous control sera averaged 11·7% for T_4, expressed as the coefficient of variation. The normal range for plasma total T_4 in our laboratory is 60 to 150 nmol/l. Plasma thyroid stimulating hormone was also measured by radioimmunoassay[16] in which the between assay coefficient of variation was 11·2%. The normal range for plasma thyroid stimulating hormone is less than 0·7 to 5·7 mU/l.

Statistical analysis used the Wilcoxon ranked sum and signed rank two-tailed test for pair differences. Correlations between left ventricular ejection fraction, heart rate, and plasma thyroxine used a linear regression coefficient with least squares method of analysis. A 5% level of confidence was considered statistically significant. All data are quoted as mean±standard error of the mean (SEM).

Results

The resting left ventricular ejection fraction was significantly less when hypothyroid (0·46±0·02) compared with the same patients when euthyroid (0·53±0·02; p<0·01) (Fig. 1). On exercise, left ventricular ejection fraction increased in the hypothyroid patients to 0·51±0·02 (p<0·05 compared with resting level). One patient (case 8) showed no change in ejection fraction on exercise and case 2 showed a modest fall from 0·53 to 0·49. All patients showed an increase in left ventricular ejection fraction on exercise when euthyroid (exercise ejection fraction 0·58±0·01; p<0·01 compared with resting levels). The rise in left ventricular ejection fraction with exercise was not significantly different between the two groups.

Resting left ventricular ejection fraction in the hypothyroid patients fell to 0·42±0·02 after intravenous propranolol and in the euthyroid patients fell to 0·48±0·02 with beta adrenoceptor blockade (Fig. 1). This represents a 9% fall in ejection fraction with propranolol when hypothyroid and when euthyroid (p<0·05). With exercise, propranolol caused a 10% fall in left ventricular ejection fraction in the hypothyroid patients and a 15% fall in the euthyroid patients (p<0·01 compared with resting levels before propranolol). Thus, propranolol attenuated the rise in left ventricular ejection fraction with exercise rather more in the euthyroid than in the hypothyroid groups.

The increase in left ventricular ejection fraction with exercise and the decrease with propranolol are summarised in Fig. 2a and 2b. There was a trend for propranolol to cause a greater attenuation of the exercise-induced rise in left ventricular ejection fraction and a greater absolute fall in left ventricular ejection fraction on exercise in the euthyroid compared with hypothyroid groups, but no statistically significant differences were identified.

Changes in Ts: LVET ratio were in close agreement with changes in left ventricular ejection fraction (Fig. 3). When hypothyroid, the ratio reduced from 0·560±0·016 at rest to 0·519±0·022 on exercise (p<0·01) in keeping with an increase in left ventricular ejection fraction. After propranolol, the resting Ts:LVET ratio increased to 0·587±0·016 (p=0·10) in

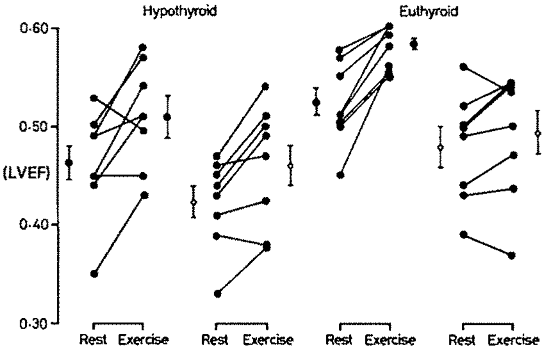

Fig. 1 *Left ventricular ejection fraction (LVEF) at rest and on exercise in the hypothyroid and euthyroid groups. The closed symbols are before and the open symbols after propranolol 0·15 mg/kg intravenously.*

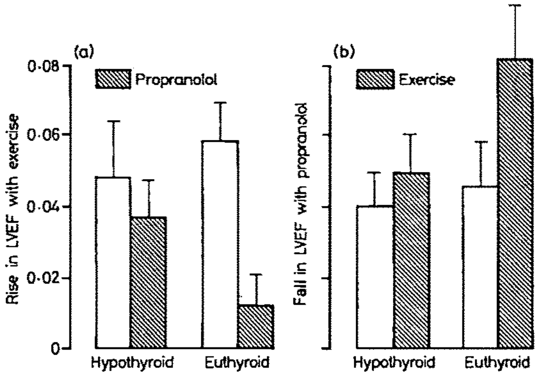

Fig. 2 *Changes in left ventricular ejection fraction (LVEF) with exercise and beta adrenoceptor blockade. The rise in LVEF with exercise before and after propranolol is shown in Fig. 2a and the fall in LVEF with propranolol at rest and on exercise is shown in Fig. 2b.*

Table 2 *Heart rate and blood pressure responses to exercise and beta adrenoceptor blockade in patients when hypothyroid and when euthyroid on thyroxine replacement treatment*

	Hypothyroid		*Euthyroid*	
	Mean heart rate (beats/min)	*Systolic blood pressure (mmHg)*	*Mean heart rate (beats/min)*	*Systolic blood pressure (mmHg)*
Rest	67±4	135±6	79±2	128±6
Exercise	97±5	167±6	106±4	167±8
Rest (propranolol)	59±4	131±6	71±4	123±5
Exercise (propranolol)	82±6	151±8	90±3	151±5

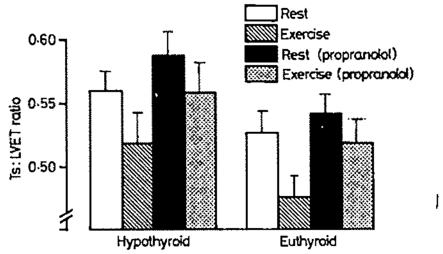

Fig. 3 *Ts:LVET ratio (see methods) in hypothyroid and euthyroid groups. A fall in the ratio indicates an increase in myocardial contractile performance.*

the hypothyroid group and the fall on exercise was somewhat reduced (0·548±0·021). In the euthyroid state the ratios were significantly less than when hypothyroid both at rest and on exercise ($p<0{\cdot}05$), but a similar reduction was seen on exercise before propranolol (from 0·527±0·018 to 0·471±0·020; $p<0{\cdot}025$) with an attenuated fall after propranolol (from 0·542±0·016 to 0·517±0·021; $p<0{\cdot}05$).

Changes in systolic blood pressure and mean heart rate are detailed in Table 2. No significant differences in resting or exercise systolic blood pressure were detectable in the two groups either before or after propranolol. Mean heart rate was reduced when hypothyroid at rest (67±4 beats/min against 79±2 beats/min euthyroid; $p<0{\cdot}01$), and on exercise (97±5 beats/min against 106±4 beats/min euthyroid; $p<0{\cdot}05$). Propranolol caused a 12% reduction in resting heart rate when hypothyroid and a 10% reduction when euthyroid. The percentage reduction in exercise heart rate with propranolol was also similar, being 10% when hypothyroid and 15% when euthyroid.

There was no correlation between left ventricular ejection fraction or Ts:LVET ratio and thyroid hormone levels in either the hypothyroid or euthyroid state. When hypothyroid, resting heart rate was related to plasma total thyroxine, the correlation coefficient ($r=0{\cdot}59$; $p<0{\cdot}05$) being improved by beta adrenoceptor blockade ($r=0{\cdot}69$; $p<0{\cdot}05$). Heart rate at rest or on exercise was unrelated to plasma total thyroxine when euthyroid.

No abnormalities in regional wall motion were detected in any patient at rest or on exercise before or after propranolol.

Discussion

Although the mode of action of thyroid hormones has not been fully elucidated, much evidence favours binding to nuclear chromatin as the principal site of action, with secondary modulation of protein synthetic pathways.[17] It is therefore not surprising that alterations in many aspects of cellular function have been reported in thyroid hormone deficiency as well as thyroid hormone excess.[18] A nuclear binding site does not, however, exclude effects on the plasma membrane or mitochondrial membrane in initiating thyroid hormone action. A reduction in beta adrenoceptor density in ventricular membranes from hypothyroid rats[11] suggests that a change in the number of catecholamine receptor sites, leading to adrenergic hyposensitivity, might be an important effect of hypothyroidism. It is far from clear, however, whether altered beta adrenoceptor density in vitro would cause a change in sympathetic sensitivity in vivo in view of the close relation between the presynaptic nerve terminal and postsynaptic myocardial cells in the regulation of inotropic and chronotropic responses to neurotransmitter release.

This study has therefore investigated myocardial contractile function in hypothyroid and euthyroid patients at rest and on exercise before and after beta adrenoceptor blockade. By using the same patients as controls, the problems of inter-individual variability are avoided. The findings suggest that there are no significant differences in left ventricular contractile responses to increased sympathetic tone (exercise) or to sympathetic blockade (propranolol) in the hypothyroid and euthyroid state. There is, however, an absolute reduction in myocardial contractile performance at rest and on exercise in hypothyroidism that is independent of beta adrenoceptor activation and is presumably a direct effect of thyroid hormone deficiency. The changes in contractile function at rest and on exercise when euthyroid are within the normal range of response in our laboratory.

Heart rate itself may be a determinant of contractile performance in man.[19] The fall in left ventricular ejection fraction in hypothyroidism might thus be partly caused by the reduction in heart rate at rest and on exercise (Table 2). We have, however, shown that increase in heart rate after vagal blockade with atropine has no effect on left ventricular ejection fraction or Ts:LVET ratio.[14] Furthermore, Wainwright *et al.*[20] showed that with incremental right ventricular pacing up to 125 beats/min, left ventricular ejection fraction progressively decreases. In the present study, exercise left ventricular ejection fraction when hypothyroid was still slightly less than resting left ventricular ejection fraction when euthyroid despite a substantially higher heart rate in the former group. It is likely therefore that there is a true reduction in myocardial contractile performance at rest and on exercise in hypothyroidism.

Both clinical[21] and necropsy[22] studies have shown that coronary artery disease occurs more frequently in hypothyroid patients than in controls matched for age, sex, blood pressure, and associated extrathyroid disorders. This agrees with experimental data to show that thyroid hormone deficiency potentiates the development of atherosclerosis in cholesterol-fed animals and that thyroid hormone administration can inhibit atherogenesis.[23] The incidence of coronary disease in our series is unknown but it is of interest that the patient in whom a clinical diagnosis of angina pectoris was made was the only patient to show a small fall in left ventricular ejection fraction on exercise in the hypothyroid state. A fall in left ventricular contractile performance on exercise is readily demonstrable in patients with coronary disease[24] and this is the probable explanation in this patient. Intriguingly, left ventricular ejection fraction increased normally in this patient when euthyroid. Histological study of the myocardium in cases of severe hypothyroidism shows non-specific changes of myofibrillar swelling, oedema, and interstitial fibrosis.[25] It is possible that irreversible impairment of cardiac function may develop in such extreme cases, though all of our patients showed a return to normal function a maximum of eight months after starting oral thyroxine.

Previous studies into the effect of propranolol on resting left ventricular ejection fraction in normal subjects have given conflicting results, with either no effect or a depressant effect on resting ventricular performance.[24 26-29] Differences are probably related to variability in drug dosage and route of administration, subject selection, and methods of assessment of contractile performance. On exercise ventricular performance is consistently depressed[29] independent of its effect on heart rate.[30 31] Our studies have shown that propranolol does not modify the pattern of change in contractile performance at rest or on exercise in the hypothyroid state. Attenuation of the exercise-induced rise in contractility was similar to that when euthyroid.

Although absorption of propranolol[32] and other drugs[33 34] is impaired in hypothyroidism, propranolol metabolism[32] and plasma protein binding[35] are not influenced by thyroid status. It is thus unlikely that there would be major differences in plasma propranolol concentrations after intravenous administration when hypothyroid or euthyroid. A reduction in peak exercise tachycardia of 16% when hypothyroid and 15% when euthyroid suggests similar functional beta adrenoceptor antagonism in both groups. The dose of propranolol used (0·15 mg/kg) has been shown to cause a 20 to 30 fold increase in the isoprenaline dose required to increase heart rate by 25 beats/min and to give plasma propranolol concentrations in the range 50 to 100 ng/ml,[36] suggesting satisfactory beta adrenoceptor blockade over the study periods.

Propranolol administration causes a fall in levels of circulating tri-iodothyronine, physiologically the most important thyroid hormone, and a rise in levels of the metabolically inactive isomer "reverse" tri-iodothyronine.[37] The drug probably acts similarly to non-thyroidal illness, either by alternative peripheral monodeiodination of thyroxine[38] or by reduction in activity of the deiodinase enzyme activity responsible for tri-iodothyronine production.[39] Though this may have important consequences in hyperthyroidism,[40] it is unlikely to contribute to the acute effects of propranolol in hypothyroidism.

Left ventricular function is reversibly depressed by thyroid hormone deficiency but responses to exercise before and during beta adrenoceptor blockade are normal. We have not shown any evidence of altered adrenergic sensitivity in the control of myocardial contractile function in hypothyroidism. This suggests that myocardial depression in thyroid failure is independent of the cardiac neurosympathetic axis. Changes in adrenoceptor density in this condition, if they occur in man, appear not to be associated with a change in functional response of the heart to altered sympathetic tone.

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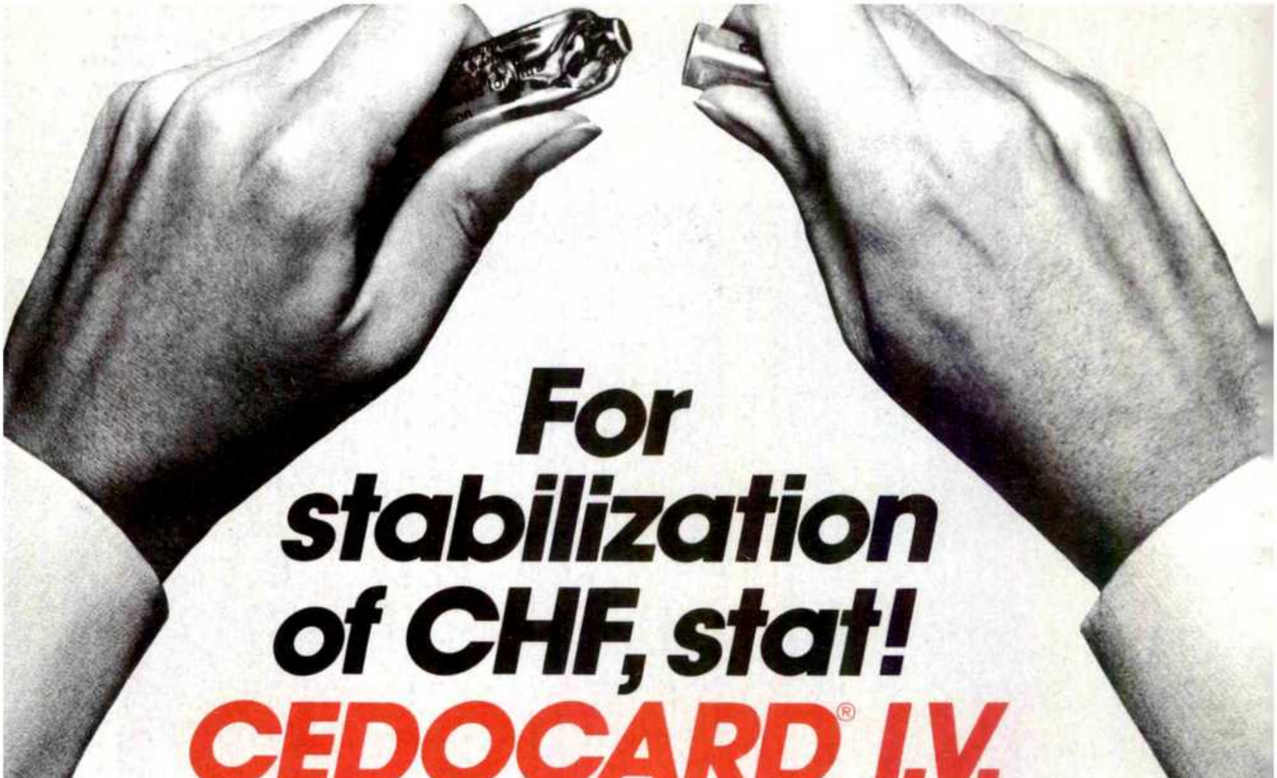

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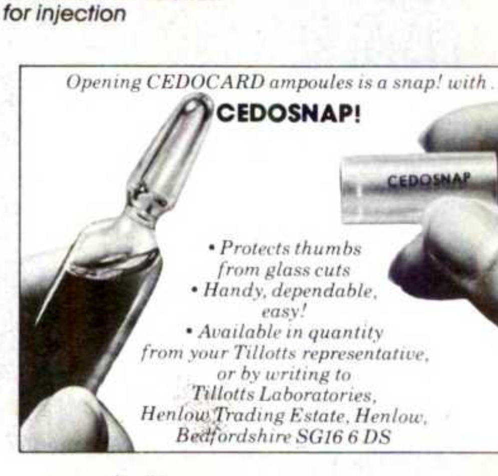

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A trial of prophylactic mexiletine in home coronary care

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SUMMARY A double blind randomised study was undertaken comparing the effects of oral mexiletine and placebo given by general practitioners at home in the early stages of suspected acute myocardial infarction, and continued for six weeks. The study comprised 216 patients. In 59 the diagnosis of acute myocardial infarction was not confirmed. Of the 72 patients with confirmed myocardial infarction treated with mexiletine, 11 (15·3%) died, compared with 19 (22·4%) of the 85 patients given the placebo, and significantly fewer of the former compared with the latter had frequent ventricular ectopics or ventricular tachycardia recorded on 24 hour electrocardiograms. Numbers of patients transferred to hospital or withdrawn from the trial because of arrhythmia or heart failure were similar in the two treated groups. Ten (13·9%) of the patients taking mexiletine had the drug withdrawn because of side effects attributed to it, compared with three (3·5%) of the group taking the placebo. A further five patients (all on mexiletine) also had treatment withdrawn because of side effects but infarction was not later confirmed. The results indicate that oral mexiletine can be given safely to patients with suspected myocardial infarction at home by their general practitioners in the absence of a positive electrocardiographic diagnosis. The frequency of ventricular tachycardia is significantly reduced; but there is no evidence of reduced mortality.

Precise figures are not available for the proportion of patients with acute myocardial infarction cared for at home in the UK. There is no reason to believe that the proportion of one-third found in the Teesside survey in 1976[1] is unusual. Sudden unexpected death from ventricular fibrillation occurs in patients looked after at home just as it does in hospital.

Apart from one study[2] using intramuscular lignocaine prophylactically for prehospital coronary care, there have been no studies on prophylactic antiarrhythmic therapy at home. General practitioners are reluctant to use drugs usually reserved for the controlled conditions of a coronary care unit. Lignocaine can be used but its parenteral route of administration poses insuperable problems in patients for whom continued home care is proposed.

We have investigated the feasibility of preventing ventricular fibrillation at home. This study was designed to determine the practicability of general practitioners giving a prophylactic antiarrhythmic agent to patients with suspected acute myocardial infarction and to determine the effects on cardiac arrhythmias and mortality. Mexiletine was chosen as being a class I antiarrhythmic agent rapidly absorbed orally with few side effects which has been shown to reduce the prevalence of ventricular arrhythmias after acute myocardial infarction.[3 4]

Method

The West Berkshire Health District centred on Reading has a mixed urban and rural population of 450 000 patients served by 202 general practitioners. One hundred and seventy-four of these general practitioners agreed to participate in the trial and they were specifically asked not to change their usual criteria for deciding what to do with patients with suspected acute myocardial infarction. If they decided to look after a patient at home they were invited to enter the patient into the trial and to use the diagnostic facilities offered. Management of the patients remained in the general practitioners' control unless a problem arose while the research registrar was with the patient. Consent for the trial was obtained from the local ethical committee.

Patients seen more than 36 hours after the onset of symptoms and those unlikely to comply with treatment were excluded, as were those who were aged over 75, or were shocked, or comatose, or who had a heart rate of less than 50 beats per minute.

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Supplies of identical active and placebo capsules in computer randomised blocks of two were distributed to all general practitioners at the onset of the trial and subsequently as the usage dictated, with the recommendation they they carry them with them when on duty. Prior informed consent was obtained verbally from the patients. After recording the basic details of pulse rate, blood pressure, analgesia given, and starting the patient double blind on a six week course of mexiletine (400 mg at once and then 200 mg eight hourly) or placebo, the general practitioner registered the patient by telephone with the Coronary Care Unit at Battle Hospital, Reading.

Each day a full time research registrar (JMT) or one of her deputies (NJCS, JRI) visited any patients registered over the previous 24 hours. The history was confirmed, details of analgesia and other cardiac drugs documented, the patient examined, a 12 lead electrocardiogram recorded, and blood taken for the measurement of both cardiac enzymes and mexiletine concentrations. In those patients in whom it was practicable, an Oxford Instruments Medilog 424 electrocardiograph recorder was connected. Relevent results were telephoned to the general practitioner at this stage and subsequently. A further visit was made the next day to repeat the observations and remove the recorder. An appointment was made for a final visit at six weeks when the patient was questioned about side effects, blood was taken for a final mexiletine concentration, and the number of capsules remaining was counted.

The collated results from the first two visits were assessed blind by one person (JMT), and on the basis of the clinical findings, the electrocardiogram, and the cardiac enzymes all patients were assigned into one of four categories.

(1) Definite myocardial infarction: Good clinical history *plus:* electrocardiographic changes (including left bundle-branch block or subendocardial infarction), *plus* a pronounced rise in enzymes ($\geq$ 50% above the upper limit of normal).

(2) Probable myocardial infarction: Good clinical history *plus:* an electrocardiogram showing new Q waves or typical subendocardial changes *and/or* a rise in enzymes above the upper limit of normal.

(3) Ischaemic heart disease: A good previous history of ischaemic heart disease but no evidence for fresh myocardial infarction.

(4) Other

For the purposes of this study, patients in categories 1 and 2 were considered as having suffered an acute myocardial infarction and this was assumed in those dying at home after taking the trial tablets but before the visit of the trial doctor. Patients in categories 3 and 4 were withdrawn from treatment as were those transferred to hospital, those with arrhythmias requiring treatment, and those with shock, coma, severe intercurrent illness, unacceptable side effects, or who were otherwise unable to take drugs orally. All such patients withdrawn from treatment were questioned at six weeks about side effects and were included in the analysis of results. Details concerning the patients who died during the six week study period were obtained from the general practitioner or occasionally the relatives. Deaths were classified as being either sudden or occurring in the context of a gradual deterioration.

Serum cardiac enzyme concentrations were estimated in the Department of Clinical Chemistry, Royal Berkshire Hospital, with upper limits of normal of 40 U (AST) and 250 U (LDH). Plasma mexiletine concentrations were measured using a specific gas-liquid chromatographic technique.[5] Twenty-four hour tape recordings were analysed on a Reynolds High Speed ECG Analyser by a trained observer who did not know which patients had been treated. Tapes with less than eight hours' analysable electrocardiogram were rejected. Ventricular arrhythmias were classified as ventricular extrasystoles (aberrant beats not preceded by P waves), frequent ventricular extrasystoles (>30 per hour), R on T ($RR^1/QT \leq 0{\cdot}85$), multifocal (two or more morphologies in any hour), couplets (two consecutive ventricular beats separated by not more than 400 ms), ventricular tachycardia (three or more consecutive ventricular beats at a heart rate more than 150 beats a minute), prolonged ventricular tachycardia (more than 10 beats a salvo), and frequent ventricular tachycardia (more than three runs in any tape). A pause was defined as a gap of 1500 ms separating two consecutive beats.

Significance testing for the differences in mortality, additional treatment received, incidence of arrhythmias, and side effects in the two groups was done using the χ^2 test, with Yates' correction. The Mann-Whitney U test was used for testing the significance of the differences in numbers of extrasystoles and enzyme levels between the two groups. Simple linear regression was used to test the correlation of blood levels with age.

Results

Over a 22 month period (November 1978 to August 1980), 222 patients were referred and 216 complied with the entry criteria (five had histories longer than 36 hours and one was aged over 75). Seventy-two of 103 patients allocated to mexiletine and 85 of 113 patients allocated to placebo had confirmed myocar-

Table 1 *Classification of entrants*

	Placebo		*Mexiletine*		*Total*
	No.	*%*	*No.*	*%*	
Entrants	*113*	*100*	*103*	*100*	*216*
Definite myocardial infarction	66	58	52	50	118
Probable myocardial infarction	19	17	20	19	39
Ischaemic heart disease	14	12	12	12	26
Other	14	12	19	18	33

dial infarction.

Table 1 shows the classification of the trial entrants according to our four diagnostic categories. Table 2 shows the baseline clinical details of the patients with myocardial infarction according to treatment group. Table 3 shows the electrocardiographic details and median peak cardiac enzymes in the two treatment groups. There were no significant differences between the two treatment groups for any of these criteria, and, other than oral analgesics which were given more frequently ($p<0·05$) within three hours of the loading dose to patients taking mexiletine, there were no differences in concurrent drug administration. Apart from beta blockers being taken by 12 out of 113 (10·6%) having placebo and 10 out of 103 (9·7%) having mexiletine, no patients were receiving any other antiarrhythmic drug. Table 4 shows the outcome for all patients.

MORTALITY

The overall mortality rate was lower in the mexiletine group (12 out of 103, 11·7%) than in the placebo group (20 out of 113, 17·7%) (NS). Two patients with unconfirmed myocardial infarction died, one one day after withdrawal from a dissecting aneurysm, and one suddenly 14 days after treatment was withdrawn. For patients with confirmed myocardial infarction, the mortality during the six week trial period was again lower in the mexiletine group (11 out of 72, 15·3%) compared with the placebo group (19 out of 85, 22·4%) (NS). Thus 30 deaths occurred in the confirmed infarct group. Of these, 13 patients were withdrawn before death and in only two of this group had mexiletine been taken within 24 hours of death.

Eleven patients (seven placebo, four mexiletine) with assumed myocardial infarction died suddenly after entry but before being seen by the project doctor. In one of these an electrocardiogram taken by the general practitioner showed early changes of infarction, but the remaining 10 patients had no electrocardiographic or enzyme evidence collected before sudden death after a story of typical chest pain.

No patients died between the project doctor's two visits while on the 24 hour electrocardiograph recorder. Six patients died after the project doctor's second visit while still in the trial, three suddenly (two taking placebo, one taking mexiletine) and three after gradual deterioration with heart failure (one taking placebo, two taking mexiletine). Of the withdrawals, nine patients with confirmed infarction on placebo died during the six week period (four suddenly and five in heart failure), compared with four on mexiletine (two suddenly and two in heart failure). Fourteen patients died suddenly while taking treatment (nine taking placebo and five taking mexiletine) (NS).

WITHDRAWALS

Forty-three (27%) patients with confirmed myocardial infarction were withdrawn for reasons given in Table 5. Twenty-four of these (14 taking placebo, 10 taking mexiletine) were transferred to hospital, mostly because of continuing chest pain or heart failure (10 taking placebo, eight taking mexiletine) and none solely because of side effects.

SIDE EFFECTS

By the second day of the trial doctor's visit 37 of 216

Table 2 *Baseline details in patients with confirmed myocardial infarction*

Total	*Placebo* *85*	*Mexiletine* *72*	*Total* *157*
(1) Sex:			
Male	72 (85%)	57 (79%)	129
Female	13 (15%)	15 (21%)	28
Mean age ± SD (y)	61·3 (8·5)	61·0 (9·4)	61·1 (8·9)
Relevant past medical history			
Nil	40	34	74
Infarct	23	19	42
Angina	21	21	42
Diabetes	3	4	7
Hypertension	18	11	29
Heart failure	5	3	8
(2) Median time between onset of symptoms and initial dose of trial drug (h)	5·17	6·14	5·85
(3) Initial pulse rate (beats/min (mean))	77·9	79·6	
Initial systolic BP (mean)	146·5	143·6	
Initial diastolic BP (mean)	87·6	87·8	

Table 3 *Classification of infarcts and enzyme results*

	Placebo		*Mexiletine*	
Total number of patients	85		72	
Median peak AST	128		161	
Median peak LDH	360		535	
Electrocardiographic pattern	Definite No.	Probable No.	Definite No.	Probable No.
Anterior full thickness	16	3	12	1
Anterior full thickness + right bundle-branch block and/or left axis deviation (−30°)	6	1	6	1
Inferior full thickness	17	3	20	0
True posterior	2	1	1	0
Left bundle-branch block	2	0	1	0
Subendocardial infarct	16	6	9	16
No definite electrocardiographic change of infarction	0	5	0	2
Electrocardiogram not recorded before patient died at home	7	0	3	0

Table 4 *Outcome for all patients admitted to study*

	Placebo		*Mexiletine*	
	No.	*%*	*No.*	*%*
Patients in study	113	100	103	100
Infarction not confirmed so withdrawn from study*	28	24·8	31	30·1
Withdrawn for other reasons† (see Table 5)	20	17·7	23	22·3
Died while taking trial drug	10	8·8	7	6·8
Completed 42 days on treatment	55	48·7	42	40·8

* Two patients died subsequently during the six week study period (see text).

† Thirteen patients died after withdrawal but during the six week study period (see text).

Table 5 *Reasons for withdrawal of patients with confirmed myocardial infarction*

	Placebo	*Mexiletine*
Heart failure	6*	6
Side effects	3	10
Chest pain	5	2
Arrhythmias	4	2
Other	2	3

*Includes one patient not transferred to hospital.

Table 6 *24 hour electrocardiographic abnormalities*

	Placebo No.	*Placebo %*	*Mexiletine No.*	*Mexiletine %*
No. of electrocardiograms analysed (≥ 8 hours)	50	(100)	38	(100)
No. with atrial ectopics	33	(66)	21	(55)
No. with supraventricular tachycardia	12	(24)	8	(21)
No. with atrial fibrillation*	7	(14)	2	(5)
No. with pauses	1	(2)	0	(0)
No. with ventricular extrasystoles	47	(94)	36	(95)
(a) frequent ventricular extrasystoles***	20	(40)	4	(11)
(b) R on T	1	(2)	1	(3)
(c) multifocal	38	(76)	28	(74)
(d) couplets	26	(52)	15	(39)
(e) ventricular tachycardia**	12	(24)	2	(5)
(f) frequent ventricular tachycardia	4	(8)	1	(3)
(g) prolonged ventricular tachycardia	2	(4)	1	(3)
(h) ventricular fibrillation	0	(0)	1	(3)

*** $p < 0{\cdot}01$
** $p < 0{\cdot}05$
* $p < 0{\cdot}325$

patients (15 taking placebo, 22 taking mexiletine) had developed possible side effects of treatment, nausea being the most common (six taking placebo, 11 taking mexiletine). In 18 patients (15 taking mexiletine, three taking placebo), unacceptable side effects alone caused withdrawal of treatment, and in five of these (all taking mexiletine) the diagnosis of myocardial infarction was not subsequently confirmed. Nineteen (45%) of the 42 patients taking mexiletine completing the trial volunteered side effects, mainly gastrointestinal upset and dizziness, compared with 12 of 55 (22%) taking the placebo ($p<0{\cdot}05$). No patient started on mexiletine and subsequently withdrawn because the diagnosis was not confirmed had any symptoms six weeks later.

24 HOUR ELECTROCARDIOGRAPHIC ANALYSES

Fifty patients with confirmed myocardial infarction taking placebo and 38 patients with confirmed myocardial infarction taking mexiletine had readable tapes with median tape lengths of 23 and 22 hours, respectively. The median delay between the onset of symptoms to the start of the tapes was 26 hours for the placebo group and 29 hours for the mexiletine group. The abnormalities found on the 24 hour electrocardiogram are shown in Table 6.

Patients with confirmed myocardial infarction taking mexiletine had fewer ventricular extrasystoles than those taking placebo (median ectopic count per hour 2·63 versus 6·09, $p<0{\cdot}05$). Serious ventricular arrhythmias, including frequent ventricular extrasystoles and ventricular tachycardia, were seen more frequently in patients in the placebo group. No differences were seen between the two groups in the incidence of pauses or supraventricular arrhythmias including atrial fibrillation. The median number of ventricular extrasystoles per hour in the 12 of the 50 patients taking placebo who had ventricular tachycardia was 14·34 compared with 3·02 in the other 38 who did not have this arthythmia ($p<0{\cdot}01$). Similarly, in the former, frequent ventricular extrasystoles (nine out of 12 compared with 11 out of 38, $p<0{\cdot}05$) and couplets (12 out of 12 compared with 14 out of 38, $p<0{\cdot}001$) were seen more frequently. Of the 12 patients on placebo who had ventricular tachycardia, seven completed the six week study, three died during the trial, and two were withdrawn because of heart failure, one to die subsequently.

DRUG PLASMA LEVELS

The mean mexiletine concentrations for patients with confirmed myocardial infarction on days 1, 2, and 42 were 0·69 μg/ml, 1·00 μg/ml, and 0·82 μg/ml, respectively. Two patients supposedly taking mexiletine had an undetectable level on day 42 (lower limit of sensitivity for the assay 0·01 μg/ml). No significant correlation was found in patients with confirmed myocardial infarction between age and blood levels on day 1, 2, or 42.

There was no significant difference in the median number of extrasystoles per hour for patients with mexiletine concentrations (mean of day 1 and day 2 concentration) of at least 0·75 μg/ml compared with those with concentrations of less that this for patients with or without confirmed myocardial infarction. The mean drug levels on day 2 in those patients subsequently withdrawn because of side effects was not significantly different from that in other patients on day 2.

Discussion

The prime function of coronary care remains the prevention and treatment of ventricular fibrillation. Lown's original prediction[6] that the detection and treatment of warning arrhythmias would reduce the frequency of ventricular fibrillation has not stood the test of time.[7] An argument can be made for effective prophylactic antiarrhythmic therapy, since significant reduction in the mortality of acute myocardial infarction will only be achieved by early intervention. Prophylactic antiarrhythmic therapy given at home has the advantage that treatment is started at the earliest opportunity and a reduction in ventricular fibrillation ought to be paralleled by a reduction in mortality.

A review of the published reports of prophylactic antiarrhythmic treatment after acute myocardial infarction suggests that treatment given early might reduce the frequency of ventricular fibrillation. Oral procainamide,[8] mexiletine,[3] and intravenous lignocaine[9] have been variously shown to cause a reduction in ventricular tachycardia[3 8] and ventricular fibrillation[9] in hospital. Intramuscular lignocaine[2] given out of hospital has been shown to reduce mortality but the same dosage repeated in hospital caused no reduction in ventricular fibrillation.[10] No clear conclusion is apparent. Studies with negative results are commoner than studies with positive results and all the latter have been extensively criticised for either design, patient selection, or interpretation. A carefully conducted trial recently published failed to show either significant reduction in serious arrhythmias or in six week mortality in patients treated with prophylactic oxprenolol or disopyramide[11] compared with placebo.

The placebo mortality of 22·4% in the present study must be compared with a six week mortality of 24% in the Nottingham trial[12] where 50% of patients were seen within three hours of the onset of symptoms. In the Tees-side survey[1] the mortality in patients seen after three hours was 15% so our mortality falls between these two figures.

We have not shown a significant reduction in mortality in patients taking mexiletine; but the reduction in arrhythmias and the fewer sudden deaths in such patients are consistent with a therapeutic benefit. Furthermore, an analysis of the deaths, the 24 hour electrocardiographic recordings, and the reasons for withdrawal do not support the possibility that the patients were harmed by being given mexiletine. The reduction in frequency of ventricular ectopics and ventricular tachycardia in our study is in keeping with the known effects of mexiletine given after acute myocardial infarction.[3 4] The effect of intravenous mexiletine on left ventricular function in normal man is slight[13 14] and in our patients the oral dosage used did not precipitate heart failure. The proportion of patients in the treatment group dying from heart failure was no more than in the placebo group, and the same was true for withdrawals from treatment because of heart failure. Similarly, our results make it unlikely that patients with atrioventricular or intraventricular conduction defects were harmed by mexiletine and this finding would support the data of McComish *et al.*[15] who reported shortening of the effective refractory period of the atrioventricular node and no effect on atrioventricular and His-Purkinje conduction time.

Published data suggest a minimum effective plasma concentration for mexiletine of 0·5 μg/ml[16] while a range of 0·75 to 2·0 μg/ml is associated with a low incidence of side effects.[17] The mean plasma drug concentrations in our patients were satisfactory on days 1 and 2 and at completion. The lowest concentrations were recorded on day 1 and it is probable that in the first few hours some of our patients had subtherapeutic plasma concentrations of mexiletine. The fixed dose and loading regimen used ensured that in sick and elderly patients toxic levels were rarely found and our figures indicate that a larger loading dose could be given safely to patients at home not under observation.

The study demonstrates the problems of home coronary care. Our 216 patients were seen at a median time of five hours after the onset of symptoms. Undoubtedly, general practitioners referred patients seen earlier to hospital rather than enter them into the trial. The overall diagnostic accuracy of the general practitioners was high and 73% of patients referred had myocardial infarction. Overall, 15% of patients with confirmed acute myocardial infarction for whom home care was intended had to be transferred to hospital.

The present study makes no attempt to compare the role of home versus hospital in coronary care. In rural communities and in cases where patients are seen initially a few hours after the onset of their symptoms, many general practitioners will elect to look after the patient at home. Though it may be premature to use prophylactic antiarrhythmic drugs in routine domiciliary practice, we cannot agree with Sloman's statement quoted recently in a leading article[18] "it is inappropriate to use such drugs as disopyramide or mexiletine in an environment outside a Coronary Care Unit where drugs are being used which can interfere with conduction, and which may produce serious side effects". The mainly negative findings of previous studies in prophylactic antiarrhythmic therapy may not apply to home care, and now that we have shown it to be both practicable and safe further evidence should be sought with regard to the benefit from earlier prophylactic administration of mexiletine or a similar drug by general practitioners at home.

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Vessel Wall in Athero- and Thrombogenesis: Studies in the USSR

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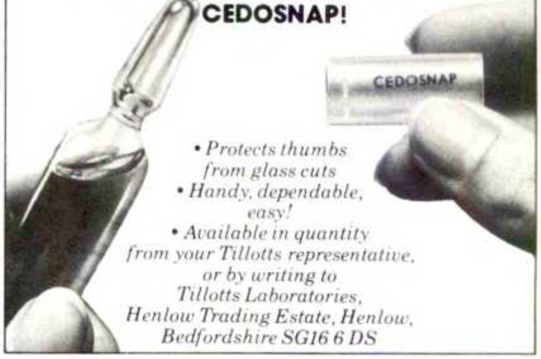

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Rupture of a papillary muscle of the tricuspid valve
Echocardiographic diagnosis

R M DONALDSON, M BALLESTER, A F RICKARDS

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SUMMARY Abnormal tricuspid valve structure and motion resulting from the rupture of a right ventricular papillary muscle were visualised by two dimensional echocardiography. These findings were confirmed at operation. Two dimensional echocardiography appears to be a satisfactory method for evaluating patients with tricuspid regurgitation of sudden onset with a view to surgery.

Rupture of the right ventricular papillary muscle is relatively rare.[1] Because the haemodynamic consequences of the resulting severe tricuspid regurgitation can often be tolerated for fairly extended periods there should be ample time for diagnosis and surgical repair of this abnormality. Cardiac catheterisation and angiography provide important information, but details of the valve are usually obscured by the simultaneous dense opacification of atrium and ventricle. We describe the visualisation of this abnormality by two dimensional echocardiography.

Case report

A 25-year-old man was admitted for postoperative cardiac assessment. He had undergone heart surgery seven years previously for correction of Fallot's tetralogy. The tricuspid valve, which was regurgitant after damage by infective endocarditis, was also surgically repaired and he remained well until six months before this admission, when he noted progressive abdominal discomfort, palpitation, and pulsating neck veins. He had signs of congestive cardiac failure and severe tricuspid regurgitation and was in intermittent atrial flutter.

Significant physical findings on admission included a conspicuously high venous pressure with a prominent systolic wave, liver distension, ankle swelling, and evidence of ascites. The blood pressure was 110/60 mmHg and he was in sinus rhythm. There was cardiomegaly with a hyperdynamic apical impulse in the fifth intercostal space internal to the anterior axillary line. There was moderate left parasternal heave, and a systolic thrill was palpable over the lower left sternal border. Cardiac auscultation disclosed evidence of residual right ventricular outflow tract obstruction and mild pulmonary regurgitation. In addition, there was a loud harsh pansystolic murmur best heard at the lower left sternal border radiating to the ventricular apex accentuating with inspiration, and an easily audible protodiastolic gallop.

The electrocardiogram documented sinus rhythm, first degree heart block, and right bundle-branch block, conduction abnormalities which had been present since surgery. There was pronounced cardiomegaly and small bilateral pleural effusions on the chest radiograph. Routine haematology and biochemistry studies were normal with the exception of the liver function tests. Blood cultures were negative.

The M-mode echocardiogram demonstrated normal left ventricular function and normal aortic and mitral valve movement and continuity. There was paradoxical septal motion and a very dilated right ventricle consistent with right ventricular volume overload. In addition, there were diastolic vibrations in the anterior leaflet of the tricuspid valve.

The two dimensional echocardiographic study using a HP77020A phased array imaging system showed similar findings, and in addition it showed frank flailing of the anterior tricuspid valve leaflet, prolapsing into an aneurysmally dilated right atrium during systole (Fig. 1 and 2). The inferior vena cava was very dilated and pulsatile; the pulmonary valve was inadequately visualised.

At cardiac catheterisation the pulmonary artery pressure was 30/8 mmHg and right ventricular pres-

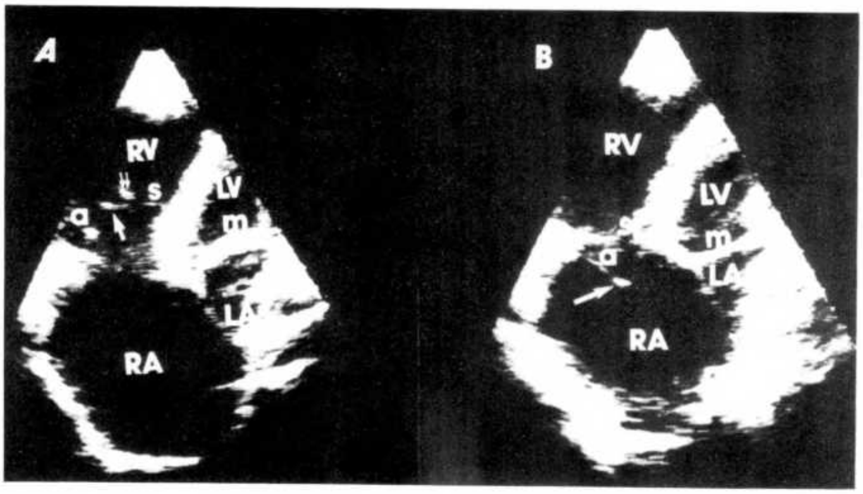

Fig. 1 *Two dimensional echocardiogram: apical four chamber view. (A) Diastolic frame: the anterior (a) tricuspid leaflet (large arrow) has a thickened tip (small arrows) and overshoots the septal (s) leaflet. (B) Systolic frame: the anterior leaflet (a) (large arrow) has a flailing systolic motion and lies within the right atrium (RA) with a loss of systolic leaflet coaptation. LA, left atrium; m, mitral valve; RV, right ventricle; LV, left ventricle.*

sure was 75/16 mmHg. The right atrial pressure was 20 mmHg with a "v" wave of 25 mmHg. There was no evidence of mitral regurgitation or a residual ventricular septal defect on left ventricular angiography. Right ventriculography showed considerable enlargement of the right ventricle, valvar and infundibular narrowing, and severe tricuspid regurgitation into the large right atrium. Pulmonary angiography was normal.

SURGERY

The right atrium was opened using a longitudinal incision. There was massive hypertrophy of the right ventricle with a small pulmonary artery and an aneurysmal right atrium. The tricuspid valve was severely regurgitant because of complete detachment of the head of the papillary muscle attaching the anterior cusp which was prolapsing into the right atrium. There was no evidence of recent infective endocarditis. The tricuspid valve was replaced by a porcine prosthetic valve and the valvar and infundibular obstruction relieved. The postoperative course was uncomplicated.

Discussion

Rupture of the right ventricular papillary muscle is rare, and occurs as a complication of right sided infective endocarditis[2] after myocardial infarction,[3] penetrating and non-penetrating chest trauma,[4] external cardiac massage,[1] and in association with primary pulmonary hypertension.[5] The increased wall tension of the dilated right ventricle resulting from residual outflow tract obstruction and an abnormal tricuspid valve probably contributed to spontaneous papillary muscle rupture in this patient. Though catheterisation and cineangiography permit the assessment of the haemodynamic state and the severity of tricuspid regurgitation, the exact underlying anatomical changes cannot usually be fully determined. Standard M-mode echocardiography and two dimensional echocardiography have been of value in the non-invasive detection of many disorders of the tricuspid valve.[6] The M-mode study permitted documentation of the right ventricular volume overload and graphically displayed the diastolic oscillations of the tricuspid valve. The latter, though non-specific,[6] suggests disruption of leaflet integrity. The echoes recorded by this method, however, are usually limited to the anterior tricuspid leaflet in systole and the rapid opening motions in early diastole. Specific spatial anatomical information was provided by the wide sector arc of two dimensional echocardiography which visualised all three tricuspid leaflets (Fig. 1 and 2). This technique permitted visualisation of non-specific features of tricuspid regurgitation such as excessive systolic pulsation of the inferior vena cava and abnormal motion of the interatrial septum. More importantly, it characterised the exact nature of the disordered valve anatomy with a normal posterior leaflet, restricted motion of the septal leaflet (caused by previous surgery), and the flail nature of the anterior leaflet.

Right ventricular papillary muscle rupture has been documented by two dimensional echocardiography only once before in a patient with active endocarditis.[7] A mobile mass of echoes attached to the tip of the chordae and the presence of tricuspid valve prolapse are very suggestive of ruptured right ventricular papillary muscle.

It may not always be possible to determine whether rupture is at muscle or at chordal level; the clinical and surgical implications of ruptured chordae, however, are similar.

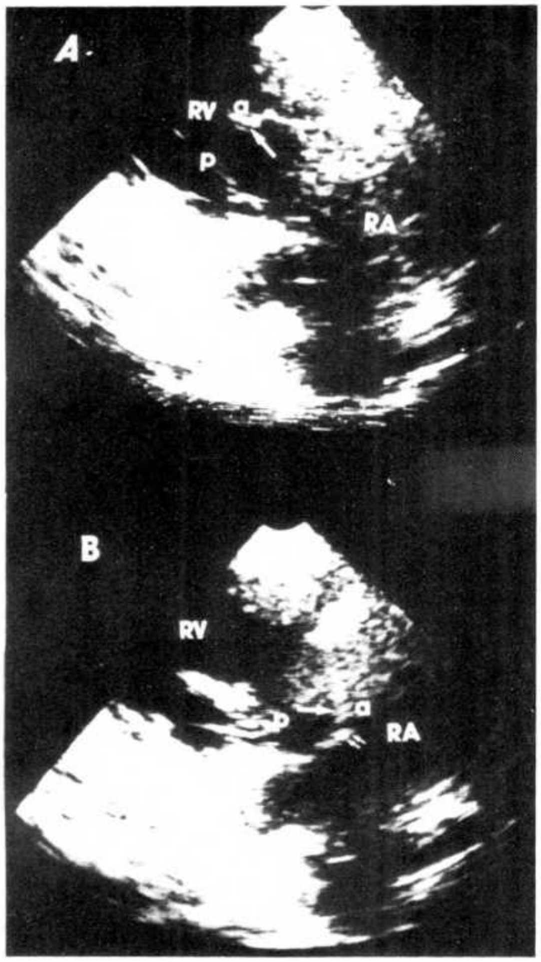

Fig. 2 *Parasternal long axis view: (A) diastolic (B) systolic frames, visualising the right atrium (RA) and inflow region of the right ventricle (RV), showing prolapse of the anterior leaflet (a) (large arrow) with a thickened tip (small arrows) suggestive of papillary muscle rupture. p, posterior tricuspid valve leaflet.*

A complete profile of the disordered valve structure can be obtained by two dimensional echocardiography and this appears to be a satisfactory non-invasive method for evaluating certain patients with tricuspid regurgitation of sudden onset with a view to surgical intervention.

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Requests for reprints to Dr A F Rickards, Department of Clinical Measurement, National Heart Hospital, Westmoreland Street, London W1M 8BA.

Br Heart J 1982; 48: 294–7

Valve replacement for severe tricuspid regurgitation caused by Libman-Sacks endocarditis

JOSEPH LAUFER, MIRA FRAND, SIMCHA MILO*

From the Department of Paediatrics "C", and the Department of Thoracic and Cardiovascular Surgery, Chaim Sheba Medical Centre, and The Sackler School of Medicine, Tel Hashomer, Israel

SUMMARY A rare case is reported of severe tricuspid regurgitation caused by Libman-Sacks endocarditis in a 9-year-old girl. The uncontrolled heart failure was successfully treated by tricuspid valve replacement.

Systemic lupus erythematosus is known to affect the heart in various ways. Though valvular involvement is common at necropsy (15 to 60%), haemodynamically significant valvular disease is extremely unusual. When reported, valvular lesions usually involve the left side of the heart, causing mitral and aortic regurgitation.[1–5] To the best of our knowledge the occurrence of severe tricuspid regurgitation in the course of systemic lupus erythematosus has not been reported. We describe such a patient who presented with severe congestive heart failure and who was successfully treated by tricuspid valve replacement.

Case report

A 9-year-old girl was admitted in February 1980 for investigation. At the age of 6 years she had begun to have febrile episodes associated with alopecia and polyarthritis. A diagnosis of rheumatic fever had been made and she had been treated with penicillin and corticosteroids for two years.

On examination she was a chronically ill and underdeveloped child. Multiple deformities of almost all joints were noted. There was no evidence of congestive heart failure. On palpation the heart was enlarged with a right ventricular heave. A blowing grade 3/6 pansystolic murmur which become louder during inspiration was heard along the left sternal border. The second sound was normally split and a short mid-diastolic murmur was present. The electrocardiogram showed sinus rhythm, incomplete right bundle-branch block, and right ventricular hypertrophy. The chest *x*-ray film showed a moderately enlarged cardiac silhouette, with right atrial and right ventricular enlargement. Echocardiography indicated right ventricular enlargement and paradoxical septal motion consistent with volume overload of the right ventricle. The tricuspid valve appeared somewhat thickened but no vegetations were seen. At cardiac catheterisation the following pressures were found: right atrium, 7 mmHg with tall V waves; right ventricle, 30/0-7 mmHg; pulmonary artery, 22/10 mmHg; pulmonary wedge pressure, 10 mmHg. A right ventricular angiocardiogram showed massive tricuspid regurgitation, but no filling defects were seen in the right ventricular cavity. Laboratory investigations confirmed the presence of lupus erythematosus cells and a positive antinuclear antibody. Erythrocyte sedimentation rate was normal.

The diagnosis of systemic lupus erythematosus with cardiac involvement was established. The patient was treated with naproxen 500 mg daily and responded well for the next two months.

In December 1980 she was readmitted, with sudden onset of severe congestive heart failure. She was apyrexial and the laboratory findings did not suggest reactivation of lupus erythematosus. Despite aggressive anticongestive therapy her condition rapidly deteriorated. Tricuspid valve replacement was advised and performed.

At operation, the pericardium was found to be very thick, oedematous, of moderately firm consistency, and adherent to the epicardium. The myocardium was grey and oedematous. The right ventricle contracted poorly. The right atrium was enlarged and its walls were thick with highly developed trabeculation. The tricuspid valve was smooth and without vegetations. Its annulus was dilated and its chordae elongated, allowing the valve to prolapse and blood to regurgitate during systole into the right atrium. The

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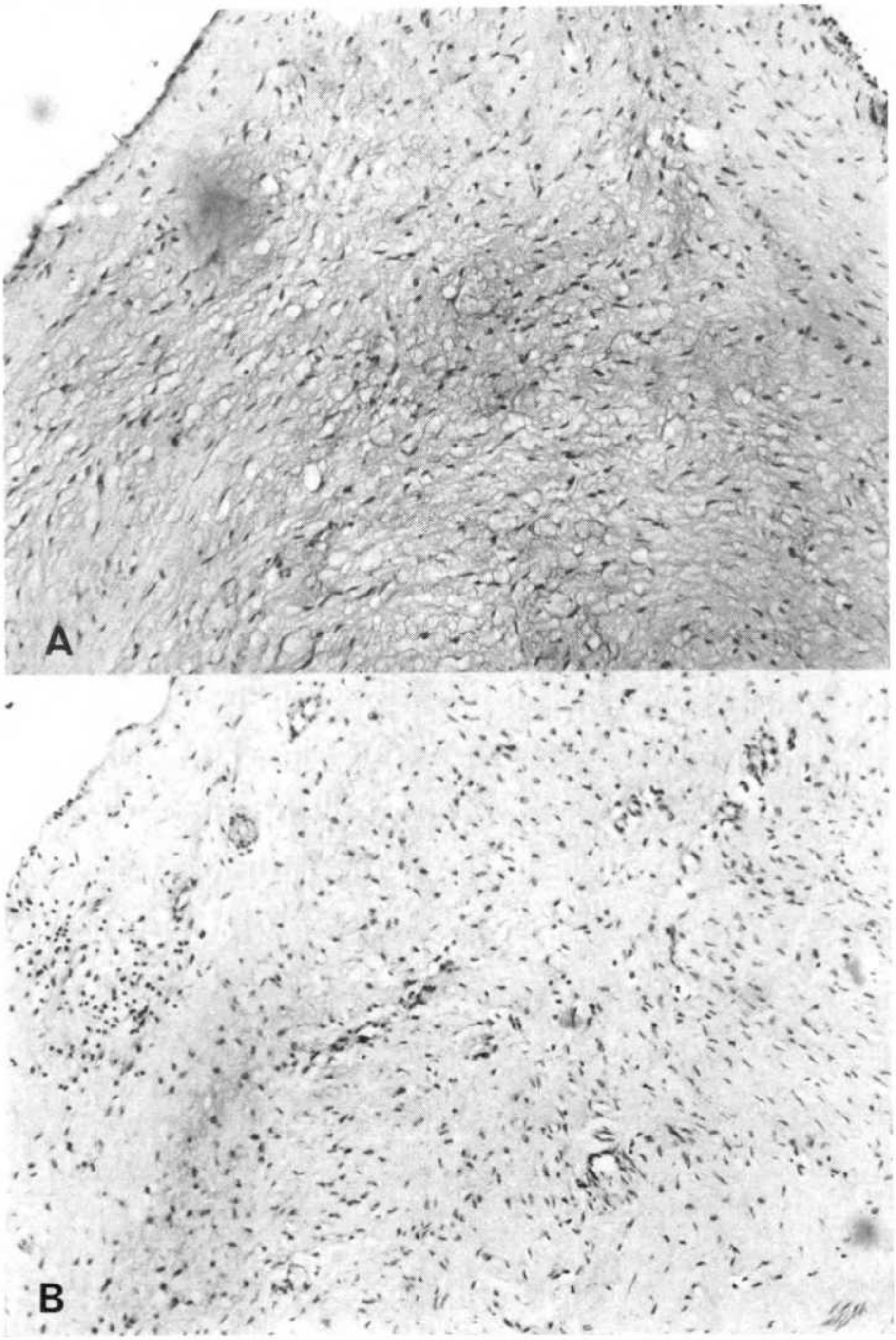

Fig. *(A) Tricuspid valve cusps contain a large amount of mucopolysaccharides, best seen in Alcian blue stain. (B) There is no fibrosis, and a focus of macrophage cell infiltration is noticed at the left side of the figure (original magnification × 100).*

subvalvular apparatus was normal. A size 27 mitral Björk-Shiley prosthesis was implanted.

Microscopical examination of the valve (Fig.) showed slight fibrosis with distinct increase in the mucopolysaccharide content of the matrix.

The postoperative course was uneventful and the patient was discharged four weeks after the operation without evidence of congestive heart failure.

Discussion

Systemic lupus erythematosus is a multisystem disease known to affect the heart in various ways. Pericarditis,[6] myocarditis,[7] endocarditis,[7-10] coronary arteritis,[9 11 12] and lesions of the conducting tissue[13] have been reported.

Libman-Sacks type endocarditis occurs in approximately half the patients with systemic lupus erythematosus.[10] It may occur without murmurs and as it is rarely associated with clinically severe valvular dysfunction the disease usually remains unrecognised during life. The clinical picture of our patient was unusual in that she was known to have had a precordial murmur for three years and she developed severe congestive heart failure despite the otherwise benign course of her systemic disease. To our knowledge, severe tricuspid regurgitation requiring valve replacement in a patient suffering from systemic lupus erythematosus has not been previously described. Though Libman and Sacks[13] stated that verrucae were most often found on the tricuspid valve, recent studies show that the mitral and aortic valves are more likely to be affected.[7 10]

It appears that the natural history of "cardiac" lupus erythematosus is changing, with the so-called healed Libman-Sacks endocarditis, an infrequent occurrence in the era before corticosteroids. The verrucae of Libman-Sacks type endocarditis are characteristically located on the ventricular mural endocardium, chordae tendineae, and papillary muscle, and usually do not distort the valve leaflets. Bulkley and Roberts,[10] however, suggested that corticosteroids promoted healing of the verrucae, either as a direct effect of the drug, or as a result of longer survival of the patients. Though vital to the management of systemic lupus erythematosus, corticosteroids have an overall deleterious effect on the heart by increasing the incidence of valvular damage.[10] In our patient the histology of the tricuspid valve was characterised by an increase in the mucopolysaccharide content of the valvular matrix. Similar findings were described by Bernhard *et al.*,[14] who considered this to be the result of corticosteroids.

Successful valve replacement has been reported in several adult patients with Libman-Sacks endocarditis of the aortic and mitral valves,[1-5 15] and the operation promptly relieved uncontrolled severe heart failure in our child. There is an analogy to the situation in children with active rheumatic carditis and severe failure because of valvar dysfunction, where the introduction of a prosthetic valve breaks the "vicious circle" and may be life saving, by allowing control to be gained over the failure and the active disease.[16] Vaughton *et al.*,[15] however, have recently warned that active verrucous endocarditis may progress and cause severe dysfunction of the prosthetic valve.

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Requests for reprints to Dr Simcha Milo, Department of Cardiothoracic Surgery, Lady Davis Carmel Hospital, 7 Michal Street, Haifa 34362, Israel.

Br Heart J 1982; **48**: 298–300

Congenital atresia of left coronary ostium

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SUMMARY A two-year-old girl, who presented with congestive heart failure and an extensive anterolateral infarction, was thought to have anomalous origin of the left coronary artery from the pulmonary artery. She improved rapidly and remained symptom free until 13 years of age, when she died suddenly. At necropsy the right coronary artery was found to be normal but in the left aortic sinus a dimple was the only remnant of the left coronary ostium. The proximal segment of the left coronary artery was diminutive and did not connect with the aortic root. This is the first report of a long term follow-up of a patient with this rare anomaly.

The majority of left coronary artery malformations are anomalies of its site of origin. The clinical picture in patients with aberrant origin of the left coronary artery from the pulmonary artery, leading to myocardial infarction and congestive heart failure in infancy, is well recognised.[1 2] We describe a patient who in infancy presented with the same clinical and electrocardiographic features, became asymptomatic later on in childhood, and died suddenly at 13 years of age. At necropsy a normally situated but atretic left coronary ostium was found.

Case report

A girl was born by normal delivery after an uneventful pregnancy, birthweight 3 kg, both parents and an older sister were healthy, and growth and development were normal until 22 months of age when anorexia, tiredness, and tachypnoea were noticed. A chest *x*-ray film, taken because a respiratory infection was suspected, showed gross cardiomegaly and increased pulmonary vascular markings. When admitted on 24 April 1969, the patient was pale, sweating, and obviously in cardiac distress. The heart rate was 160/min and the respiratory rate was 68/min. The face was puffy and the liver was palpable 6 cm below the costal margin. On palpation a heaving left ventricular impulse, displaced to the mid-axillary line, was felt. A grade 2/6 systolic murmur and a loud gallop were heard at the apex. The electrocardiogram (Fig. 1) showed sinus rhythm and a mean frontal QRS axis of +30°. Deep Q waves and sharply inverted T waves were seen in I, aVL, and the left precordial leads. In V3 and V4 the ST segment was much raised. The diagnosis was anterolateral myocardial infarction, probably caused by anomalous origin of the left coronary artery from the pulmonary artery. After two weeks of treatment with digoxin and diuretics, the tachypnoea, tachycardia, and hepatomegaly disappeared and the patient was discharged.

She was readmitted for cardiac investigation at 2½ years of age. The apex beat was displaced and a soft systolic murmur was heard at the fourth left intercostal space. There were no signs of congestive heart failure. The electrocardiogram showed the same Q waves but the ST elevation had disappeared.

Right and left cardiac catheterisation (Table) disclosed normal pressures, with the exception of a slightly raised pulmonary capillary venous (mean 14 mmHg) and left ventricular end-diastolic pressure (12 to 18 mmHg). Oximetry showed no evidence of left-to-right shunting. Angiography of the aortic root showed absence of a left main coronary artery and a large, slightly tortuous right coronary artery. Branches of the left coronary artery were seen to fill from the right side, but the proximal segment of the left coronary artery was not seen. There was no passage of contrast material into the pulmonary artery. Though direct proof of the connection was lacking, the angiograms were thought to confirm the diagnosis of anomalous left coronary artery originating from the pulmonary artery.

The patient remained symptom free and was examined at yearly intervals. When last seen in March 1980, physical examination was unremarkable. The electrocardiogram (Fig. 1) disclosed deep but narrow Q waves and T inversion from V4 to V6. In V4 the ST segment was slightly elevated. On the chest *x*-ray film

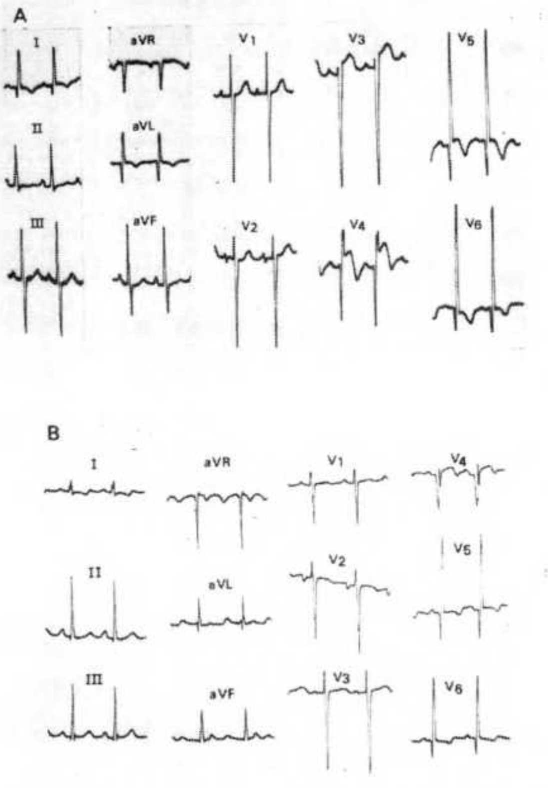

Fig. 1 *The electrocardiogram at 22 months of age (A) shows deep Q waves and inverted T waves in I, aVL, V5, and V6. The ST segment is much raised in V3 and V4. At 12 years of age (B) the Q waves persist but the ST alterations are less conspicuous.*

Table *Haemodynamic data (at age 2 years 6 months)*

Site	*Pressure (mmHg)*	*Oxygen saturation (%)*
Superior vena cava		68, 67
Right atrium	a 5 v 4 m 3	66, 69
Right ventricle	30/5	66, 66
Pulmonary artery	30/15 m 23	67, 65
Pulmonary capillary	m 14	
Left ventricle	120/12–16	
Aorta	120/65	99

the heart was normal. The M-mode echocardiogram showed a slight increase of the end-diastolic left ventricular dimension (43 mm) and the fractional shortening of the left ventricle with systole was decreased (23%). The left atrial dimension (23 mm) and the thickness of the left ventricular posterior wall (7 mm) and interventricular septum (8 mm) were normal. Exercise testing (maximum load 600 kpm/min during 1 min) provoked no chest pain. There was no ST segment depression but the T waves in V4 to V6, which were negative at rest, became positive.

On the basis of these results it was felt that cardiac surgery and a saphenous vein graft could be postponed for a few years. The patient remained symptom free. At 13 years of age she died at home suddenly. One morning she was found pale, unconscious, and gasping. She was given mouth-to-mouth respiration and rushed to the emergency department of the hospital but was dead on arrival. The days before her death she had had a slight fever, probably unrelated to the fatal outcome.

At necropsy the right coronary artery was found to arise normally from its coronary sinus. In the left aortic sinus a dimple was the only remnant of the left coronary ostium. The proximal segment of the left coronary artery was diminutive. Before the heart was opened, a coronary angiogram with injection of the right coronary artery (Fig. 2) was performed. After

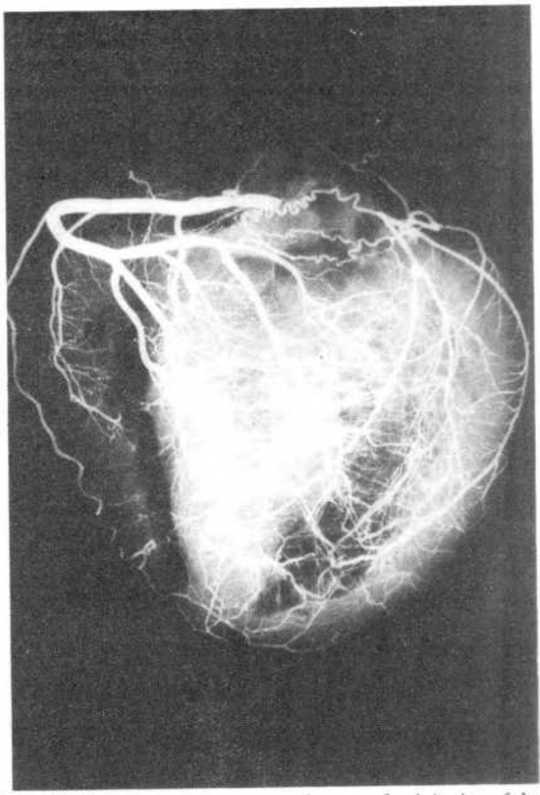

Fig. 2 *Postmortem coronary arteriogram after injection of the right coronary artery. Numerous small collaterals produce retrograde filling of the left coronary artery. Its main stem, however, is short and small and does not communicate with the coronary ostium.*

opacification of the large and slightly tortuous right coronary artery, the branches of the left coronary artery were seen to fill retrogradely via collaterals. Even at the point of maximum filling the branches of the left coronary artery were distinctly smaller than those of the right. The main stem of the left coronary artery was very short and narrow and did not communicate with the normally situated but atretic coronary orifice. Transverse sections of the heart showed a large (2×3 cm) fibrotic scar in the anterior and apical wall of the left ventricle. The entire left ventricular endocardium appeared thickened and fibrotic. The major histological finding was a zone of fresh infarction in the interventricular septum, characterised by interstitial oedema, eosinophilic coloration of the sarcoplasma, and pyknosis of cell nuclei.

Discussion

Atresia of the left coronary ostium is a rare congenital anomaly. To our knowledge, five similar cases have been reported.[3-7] The clinical picture in our case and in two previously reported infants[3 4] was indistinguishable from that observed in anomalous origin of the left coronary artery from the pulmonary artery. As characteristically seen in the latter condition, our patient presented with congestive heart failure, massive cardiac dilatation, and anterolateral infarction in infancy, with Q waves and ST elevation in I, aVL, and the left precordial leads.[1 2]

A unique feature of our case is the duration of follow-up from an episode of myocardial infarction in infancy to adolescence. Between three and 13 years of age the patient was symptom free and had a normal exercise tolerance. The cardiac volume on the chest *x*-ray film had become normal.

Cardiac catheterisation may contribute to the differential diagnosis if oximetry discloses a left-to-right shunt in the pulmonary artery. By contrast with older children with anomalous origin of the left coronary artery, however, infants with this anomaly rarely have a significant increase of oxygen saturation in the pulmonary artery.[2] Only angiography, carefully interpreted, permits an accurate diagnosis. In our case opacification of a large right coronary artery and failure to fill the left coronary artery after aortic root injection were thought to corroborate the diagnosis of anomalous origin of the left coronary artery. The non-opacification of the main stem of the left coronary artery was attributed to poor collateral circulation. The same mistake was made in the two reported infants.[3 5] We therefore suggest basing the diagnosis of anomalous origin of the left coronary artery on the visualisation of the anomalous connection after retrograde filling, which is possible in most cases,[2] and not only on the non-opacification of the left coronary artery after injection of the aortic root. Failure to show the left main coronary artery after retrograde filling from the right coronary artery strongly suggests atresia of the left coronary ostium.

Judging from the postmortem angiograms, the anomaly in our patient was probably not amenable to surgery. The small calibre of the main stem and major branches of the left coronary artery precluded the construction of a saphenous vein graft. Successful surgical correction and hence creation of a two coronary system have been reported in one adolescent[4] and one adult[7] who both presented with long standing angina pectoris.

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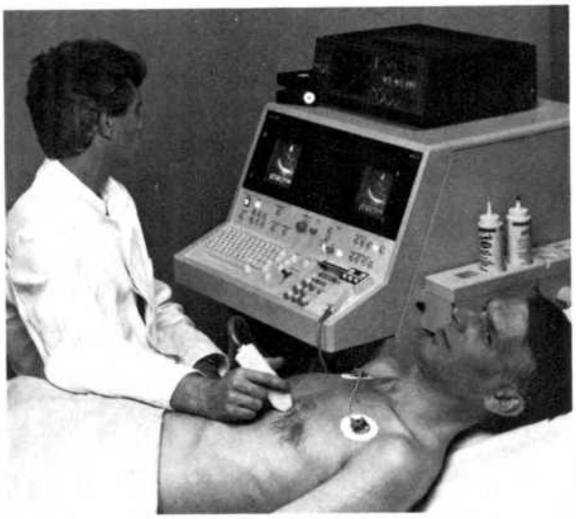

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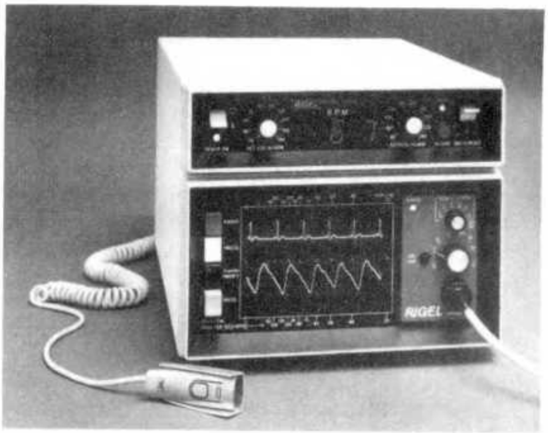

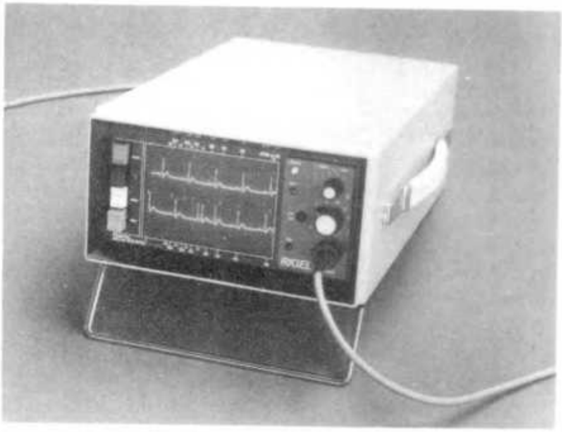

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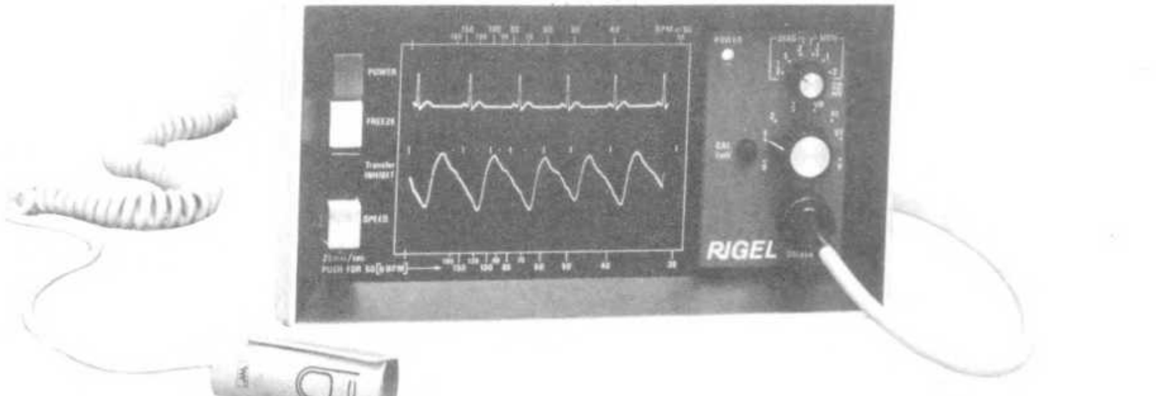

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Br Heart J 1982; **48:** 301

Mitral valve prolapse and coronary artery spasm

Sir,
I read with interest the article on Prinzmetal's angina and coronary artery spasm by Huckell and coworkers (*Br Heart J* 1981; 45: 649–55). The authors mentioned the association of mitral valve prolapse in eight of their 18 patients with Prinzmetal's angina, and wondered whether this finding was causative or coincidental, or whether patients with mitral prolapse were more prone to develop coronary artery spasm. That there is indeed a causal relation between mitral valve prolapse and coronary artery disease with or without spasm has been fairly well established.[1-3] Mitral valve prolapse, on one hand may result from coronary artery disease,[1] but on the other hand may also be responsible for inducing coronary artery spasm.[2] Mitral valve prolapse, therefore, may be either secondary or primary or both.[3]

I found that secondary mitral valve prolapse accompanying coronary artery disease has not only a different clinical auscultatory presentation[1] but a different angiographic appearance from primary mitral valve prolapse.[4] On a left ventriculogram in the 30 degree right anterior oblique projection the mitral valve in primary mitral valve prolapse has the appearance of a "bird's beak" because of the billowing of the redundant and voluminous mitral leaflets. In secondary mitral valve prolapse caused by coronary artery disease, the mitral valve on left ventriculography in the same projection has the appearance of a "nipple" because of the uneven tethering of a structurally normal mitral valve by the dysfunctional papillary muscles. This angiographic sign was present in 90% of the cases I studied.[4]

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This letter was shown to Dr Huckell who replies as follows.

Sir,
We agree that a causal relation between mitral valve prolapse and coronary artery disease with and without spasm has been reasonably established.[1-3] Our study reviewed the clinical course of our patients with coronary artery spasm and only secondarily looked at the instance of mitral valve prolapse in the same patient. We reviewed the angiographic appearance of the prolapse in the eight patients with this finding. Several did have a "nipple" appearance as described by Cheng[4]; in the majority, however, the appearance of the prolapse was not clearly definable as either a "beak" or "nipple". Nevertheless, we feel that most, if not all, of our patients with mitral valve prolapse probably have this because of papillary muscle dysfunction.[5] Further attention to the presence of either primary or secondary mitral valve prolapse in patients with coronary artery disease would be useful to see if either type of mitral valve prolapse has a predilection for coronary artery spasm.

Victor F Huckell,
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Correspondence

Br Heart J 1982; **48**: 302–3

Hang-out time of pulmonary valve in d-transposition of great arteries

Sir,
I note that in the March issue of the *British Heart Journal* Dr Fouron and his colleagues once more used the term "d-transposition of the great arteries". I have written previously expressing concern at the possible misuse of this term, but from the fact that Dr Fouron and his colleagues continue to use it, and also from discussions and correspondence with many colleagues, I know that my previous letter failed to express adequately the point I was trying to make. There is nothing wrong with the term "d-transposition" when it is used to describe a heart with the aorta arising from a morphologically right ventricular chamber, the aortic valve being to the right of the pulmonary valve. This is the fashion in which, as Dr Fouron and his colleagues pointed out in their response to my previous letter, the term is used by Dr Van Praagh and his colleagues. In their previous letter Dr Fouron and his colleagues went on to say that complete transposition was a physiological designation. I would submit that their present article describes exactly such a physiological situation. If I understand their article correctly, they are not describing results pertinent to all patients who might have a right-sided aorta arising from a morphologically right ventricle. This of course could include patients with tricuspid atresia and transposition, patients with double inlet ventricle and transposition, and even some patients with physiologically corrected transposition in situs inversus. I do not believe that it is the intention of the Montreal group to imply that their results are applicable to all these patients, who could correctly be stated as having "d-transposition". What I believe the Montreal group are describing are findings pertinent to patients having complete transposition. Indeed, throughout the rest of their paper they simply use the term "transposition of the great arteries". My previous letter gave considerable scope for misinterpretation. Indeed, I know from correspondence that it was widely misinterpreted. All I was trying to say was that, for the patients described by Dr Fouron and his colleagues, "complete transposition" is a scientifically accurate and appropriate term. "d-transposition" may apply to the majority of the patients, but it does not describe all of them, and certainly describes many patients who do not fall within the group described by the Montreal investigators. I therefore stand by my earlier contention that, for the overall group of patients—patients with atrioventricular concordance and ventriculoarterial discordance—complete transposition is a more appropriate term than "d-transposition".

R H Anderson,
Cardiothoracic Institute,
Fulham Road,
London SW3 6HP.

This letter was shown Dr Fouron and his colleagues who reply as follows.

Sir,
In his letter, Professor R H Anderson deplores once again the use of d-transposition (d-TGV) in our article on "Hang-out time of pulmonary valve in d-transposition of great arteries".[1] We agree with Professor Anderson that d-TGA means cases of TGA in which the aortic valve lies to the right (dextro or D) relative to the pulmonary valve. When d-TGA is used without further qualification, however, the typical situation, that is TGA {S, D, D}, (TGA with situs solitus and D-loop) is meant as in all patients in our series and as in 95% of necropsied cases. Hence d-TGA is convenient shorthand. When other malformations are present they must be mentioned, as for instance tricuspid atresia with d-TGA. Patients with physiologically corrected transposition in situs inversus should be described as having situs inversus (I), ventricular D-loop (D), and d-transposition of the great arteries (D), or simply {I, D, D}. We believe that anatomical precision is important physiologically

and surgically. The segmental approach to the diagnosis of congenital heart disease applies acurately in all anomalies, no matter how complex.

Reference

1 Fouron JC, Douste-Blazy MY, Ducharme G, van Doesburg N, Davignon A. Hang-out time of pulmonary valve in d-transposition of great arteries. *Br Heart J* 1982;47:277–80.

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This correspondence is now closed. Ed.

Correspondence

Br Heart J 1982; **48**: 304–5

Effects of prostaglandin E1 and other vasodilator agents in pulmonary hypertension of scleroderma

Sir,

Guadagni *et al.*[1] have recently reported the haemodynamic effects of prostacyclin in pulmonary hypertension. We report here the effects of prostaglandin E1 (PGE1) in the treatment of pulmonary hypertension in a patient with scleroderma.

A 25 year old woman with scleroderma was admitted to hospital in February 1980 for assessment of pulmonary hypertension. An open lung biopsy in January 1979 showed distinct changes in the small to medium sized muscular pulmonary arteries, with intimal fibrosis and medial hypertrophy. Neither plexiform lesions nor parenchymal fibrosis was found. In May 1979, the pulmonary arterial pressure was raised at 80/35 mmHg (mean 54 mmHg) and the pulmonary arteriolar resistance was 650 dynes s cm^{-5}. An intravenous infusion of nitroprusside at a dose of 6 μg/kg per min lowered pulmonary arterial pressure by 26% and pulmonary arteriolar resistance by 50%. Phentolamine, 5 mg intravenously, produced a 20% reduction in pulmonary arterial pressure and 13% reduction in pulmonary arteriolar resistance. The patient was placed on oral phentolamine 250 mg daily in divided doses but developed progressive dyspnoea.

On examination, the chest was normal. The jugular venous pressure was raised and a left parasternal heave was present. Skin over the fingers and toes was tight and bound down and multiple digital ulcerations were present. Telangiectasia were present on the face. Antinuclear factor was positive to a titre of 1/200.

Right heart catheterisation was performed with a Swan-Ganz catheter. Cardiac output was assessed with the thermodilution technique using a bedside cardiac output computer (Edwards Laboratories). Diazoxide was given by bolus injection through the right atrial port. PGE1 (Upjohn Company of Canada) was infused through the right atrial port for 10 minutes out of each hour for a total of 49 infusions. The initial dose was 1 ng/kg per min for 10 minutes increasing to a maximum tolerated level of 32 ng/kg per min for 10 minutes. The haemodynamic effects of PGE1 were assessed just before the final infusion of 32 ng/kg per min and immediately after completion of this infusion. Between treatment with diazoxide and PGE1, haemodynamic measurements were allowed to return to baseline values.

The right atrial pressure was 14 mmHg. Pulmonary arterial pressure was 75/34 mmHg (mean 51 mmHg), cardiac index 2·33 l/min per m^2, and stroke index 23 ml/beat per m^2. The catheter tip could not be made to flow into the wedged position and thus the total pulmonary resistance index was calculated instead of pulmonary arteriolar resistance. Diazoxide produced an increase in pulmonary arterial pressure to 85/39 mmHg (mean 60 mmHg) but a 24% decrease in systemic vascular resistance. PGE1 did not affect pulmonary arterial pressure, but just before the last infusion there had been a 23% increase in total pulmonary resistance index from 1751 dynes s $cm^{-5} \cdot m^{-2}$ to 2153 dynes s $cm^{-5} \cdot m^{-2}$ and a fall in stroke index of 22%.

The failure of intravenous diazoxide to reduce pulmonary arterial pressure suggests progression to fixed pulmonary hypertension and may explain the lack of response to PGE1. This differs from the previous reports suggesting that prostaglandins may ameliorate haemodynamic measurements in pulmonary hypertension.[1-4] On the other hand, studies in normal humans have also been variable, with PGE1 producing either a slight rise[5] or fall[6] in pulmonary arterial pressure or resistance. These results suggest that the effect of PGE1 on the pulmonary circulation in man remains to be clarified.

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Canada.

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1 Guadagni DN, Ikram H, Maslowski AH. Haemodynamic effects of prostacyclin (PGI2) in pulmonary hypertension. *Br Heart J* 1981; 45: 385–8.

Clinical features

All the babies presented with cyanosis during the first six hours of life. None had a murmur save case 5 in whom a soft systolic murmur was heard at the upper left sternal border. In cases 2 and 6, the liver was enlarged below the right costal margin by 2 and 5 cm, respectively. The electrocardiogram showed signs of right ventricular hypertrophy in all except case 4. In all cases the chest radiograph showed a heart of normal size. The lung fields had a fine granular appearance in all save cases 1 and 4. At cardiac catheterisation the pulmonary arterial pressure was equal to, or exceeded, the systemic arterial pressure and the arterial oxygen saturation was similar in the pulmonary artery and aorta in all cases (Table). In five cases pulmonary angiography showed total anomalous pulmonary venous return to an infradiaphragmatic site, except in case 4, where the left upper lobe only drained into a left superior vena cava. In the remaining case (case 5) a diagnosis of total anomalous pulmonary venous return to the right atrium was made by two dimensional echocardiography.

Four babies died at or soon after surgical repair of the anomaly at between 1 and 6 days of age. Cases 4 and 5 died before operation could be attempted. The interatrial defect was a secundum atrial defect found at operation in cases 2, 3, and 6, and a stretched foramen ovale was present in cases 1, 4, and 5.

At necropsy, in four of the cases with infradiaphragmatic total anomalous pulmonary venous return, the descending vertical vein entered the porta hepatis, and in the fifth case (case 1) it entered the inferior gastric vein. The ductus arteriosus was or had been patent in all cases, having been ligated in those patients submitted to operation. Case 1 also had a small subaortic ventricular septal defect measuring 3 mm in diameter and partial juxtaposition of the left atrial appendage. In all cases the left ventricle was of normal size.

Pathological studies

The pulmonary vessels were injected in only two patients, cases 4 and 5. The pulmonary arteries were injected under pressure with a barium sulphate gelatin mixture in the right lung of case 4 and in the middle and lower lobes of the right lung in case 5. The pulmonary veins of the right upper lobe in case 5 were also injected using the same technique. The lungs of these two cases were fixed by injecting the airways with formol saline at constant pressure. Blocks of tissue 1 cm square were taken for histological examination from the lungs of all cases, as indicated in Fig. 1.

Table *Clinical data*

Case No.	*Diagnosis*	*Age at cardiac catheterisation (d)*	*Pulmonary arterial or right ventricular pressure (mmHg)*	*Systemic arterial or left ventricular pressure (mmHg)*	*% O_2 saturation*		*Age at death (d)*
					Pulmonary artery	*Aorta*	
1	Infradiaphragmatic total anomalous pulmonary venous return	1	85/50 $\overline{60}$	75/50 $\overline{60}$	60	62	1
2	Infradiaphragmatic total anomalous pulmonary venous return	1	40/30 $\overline{33}$	45/35 $\overline{38}$	62	65	2
3	Infradiaphragmatic total anomalous pulmonary venous return	3	55/3	59/35 $\overline{43}$	64	67	3
4	Infradiaphragmatic total anomalous pulmonary venous return	3	95/55 $\overline{70}$	55/40 $\overline{45}$	64	64	4 No operation
5	Total anomalous pulmonary venous return to right atrium	3	70/50 $\overline{56}$	70/50 $\overline{56}$	61	56	5 No operation
6	Infradiaphragmatic total anomalous pulmonary venous return	5	90/69 $\overline{70}$	80/55 $\overline{60}$	69	62	6

Br Heart J 1982; **48:** 513–24

Total anomalous pulmonary venous return
Prenatal damage to pulmonary vascular bed and extrapulmonary veins

SHEILA G HAWORTH

From the Department of Paediatric Cardiology, Institute of Child Health, Guilford Street, London

SUMMARY To investigate the possibility that pulmonary vascular disease may be present at birth in children presenting with obstructed total anomalous pulmonary venous return in the neonatal period, pulmonary vascular structure was analysed in the lungs of six babies who died during the first week of life. Five babies had infradiaphragmatic total anomalous return and in one the pulmonary veins drained to the right atrium. In all cases mean percentage arterial medial thickness was greater than is normal at 5 hours. The most striking change occurred in the intra- and extrapulmonary veins. Within the lung, in all six cases mean percentage vein wall thickness was significantly increased and in two cases intimal proliferation occurred in preacinar veins. The extrapulmonary veins were generally small in all five cases of infradiaphragmatic total anomalous pulmonary venous return, microscopically were abnormally thick walled in four, and showed intimal proliferation in three cases. In two cases the descending vertical vein was severely narrowed or occluded.

A prenatal increase in intrapulmonary arterial and venous muscularity may encourage episodic pulmonary hypertension in the immediate postoperative period. In the infradiaphragmatic type of anomaly, prenatal structural changes in the extrapulmonary veins may predispose to the later development of pulmonary vein stenosis despite a successful surgical repair.

The mortality rate for correction of total anomalous pulmonary venous return has improved considerably during the past 10 years. Two recent series quote a hospital survival rate of 87%[1] and 88%.[2] Age is becoming less important as a determinant of survival probably because of earlier patient referral and improvements in surgical technique. In one recent study age was shown to have no effect on survival.[1] At The Hospital for Sick Children, Great Ormond Street, however, during the past five years the hospital survival rate for children aged 1 week or more was 87% while for those less than 1 week of age it was only 36%. The higher mortality in the younger age group may perhaps be the result not of age itself but of other factors associated with the early development of pulmonary venous obstruction. Little is known about the state of the pulmonary vascular bed at birth in these babies, but, in slightly older patients, pulmonary vascular disease has been considered to be an important determinant of survival.[3–5]

In order to investigate the possibility that pulmonary vascular disease may be present at birth in children presenting with obstructed total anomalous pulmonary venous return in the neonatal period, pulmonary vascular structure has been analysed in the lungs of six babies who died during the first week of life. Previous pathological studies on the lung in total anomalous pulmonary venous return have concentrated on pulmonary arterial structure.[5 6] Recently, however, there have been several clinical reports of pulmonary vein stenosis developing in patients who have had an apparently successful repair of the anomalous venous drainage.[1 2] The stenosis developed in the pulmonary vein, proximal to the anastomosis between the venous confluence and the left atrium, and was not related to the suture lines. In the present study, therefore, the structure of the intra- and extrapulmonary veins has been analysed in addition to that of the arteries.

SGH is supported by the British Heart Foundation.

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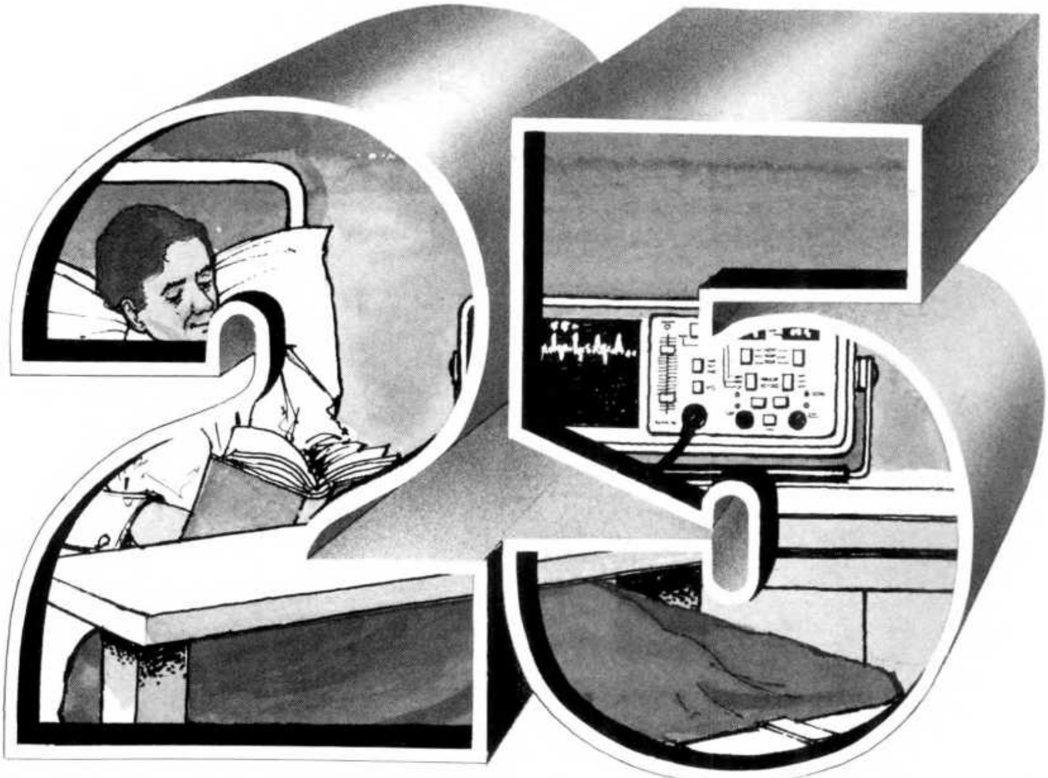

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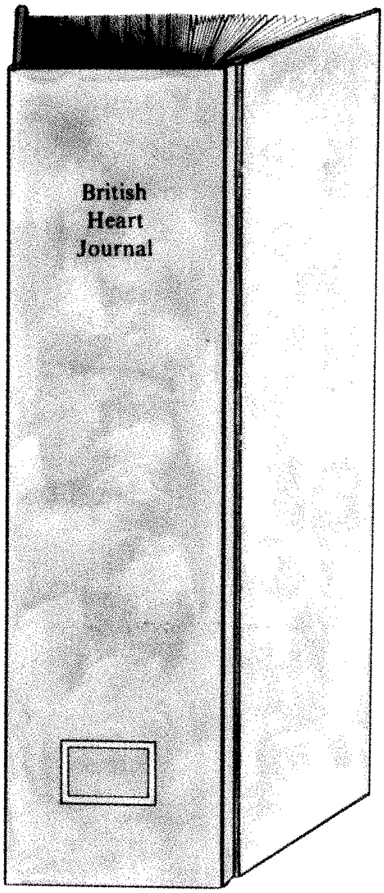

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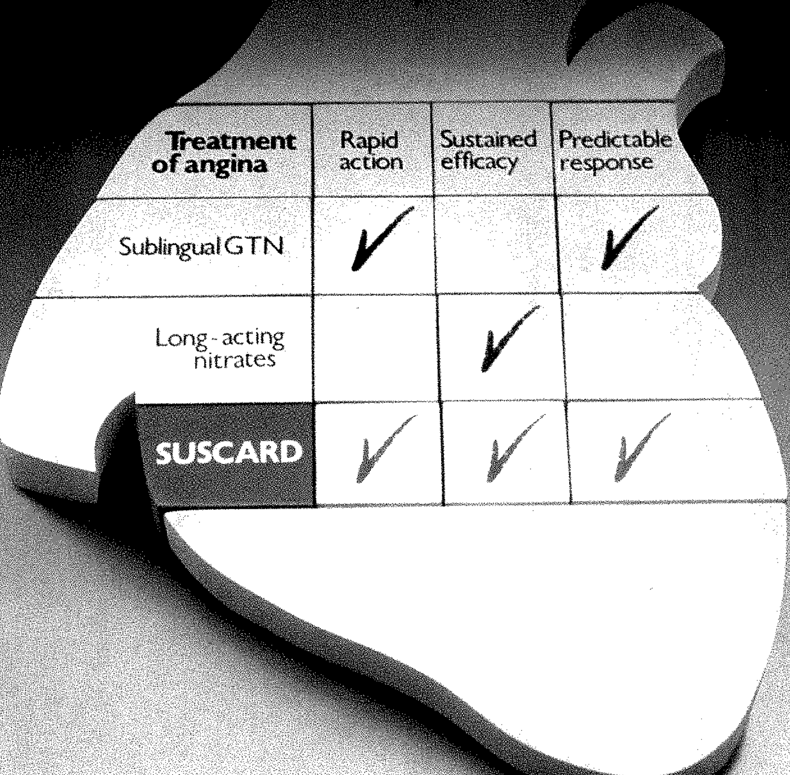

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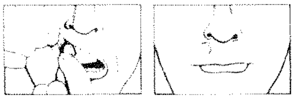

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41**: 263–7.

(2) *Books and other monographs:*
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December 1982 Vol 48 No 6

British Heart Journal

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Total anomalous pulmonary venous return. Prenatal damage to pulmonary vascular bed and extrapulmonary veins *Sheila G Haworth* 513

Computer analysis of cardiac contractility variables obtained by M-mode echocardiography in normal newborns *R Hofstetter, A Mayr, G von Bernuth* 525

Clinical, echocardiographic, and operative findings in active infective endocarditis *T H Pringle, S W Webb, M M Khan, H O J O'Kane, J Cleland, A A J Adgey* 529

Preoperative echocardiographic diagnosis of anterior mitral valve leaflet fenestration associated with infective endocarditis *M Matsumoto, J Strom, H Hirose, H Abe* 538

Haemodynamic and hormonal effects of captopril in primary pulmonary hypertension *H Ikram, A H Maslowski, M G Nicholls, E A Espiner, F T L Hull* 541

Transmural, haemorrhagic myocardial infarction after intracoronary streptokinase. Clinical, angiographic, and necropsy findings *D G Mathey, J Schofer, K-H Kuck, U Beil, G Klöppel* 546

Sudden versus gradual withdrawal of sotalol in ambulant patients with ischaemic heart disease *A Henderson, J Errington* 552

Projection of ST segment changes on to the front of the chest. Practical implications for exercise testing and ambulatory monitoring *K M Fox, J Deanfield, P Ribero, D England, C Wright* 555

Precordial ST segment depression in patients with inferior myocardial infarction: clinical implications *J S Gelman, A Saltups* 560

Complete transposition of great arteries with coarctation of aorta *O Milanesi, G Thiene, R M Bini, P A Pellegrino* 566

Accuracy and reliability of two indirect ambulatory blood pressure recorders: Remler M2000 and Cardiodyne Sphygmolog *D J Fitzgerald, W G O'Callaghan, R McQuaid, K O'Malley, E O'Brien* 572

Normal coronary arteriogram. An avoidable test? *C Ilsley, A Stockley, D Clitsakis, C Layton* 580

Sinus node function in first three weeks after cardiac transplantation *A F Mackintosh, D J Carmichael, C Wren, R Cory-Pearce, T A H English* 584

Irreversible morphological changes contributing to depressed cardiac function after surgery for chronic aortic regurgitation *R M Donaldson, R Florio, A F Rickards, J G Bennett, M Yacoub, D N Ross, E Olsen* 589

Case reports

Two dimensional echocardiographic diagnosis of partial papillary muscle rupture *R A Nishimura, C Shub, A J Tajik* 598

Anomalous low insertion of right superior vena cava *R M Freedom, M S Schaffer, R D Rowe* 601

Correspondence 604

Notices 606

Index 607

British Medical Association

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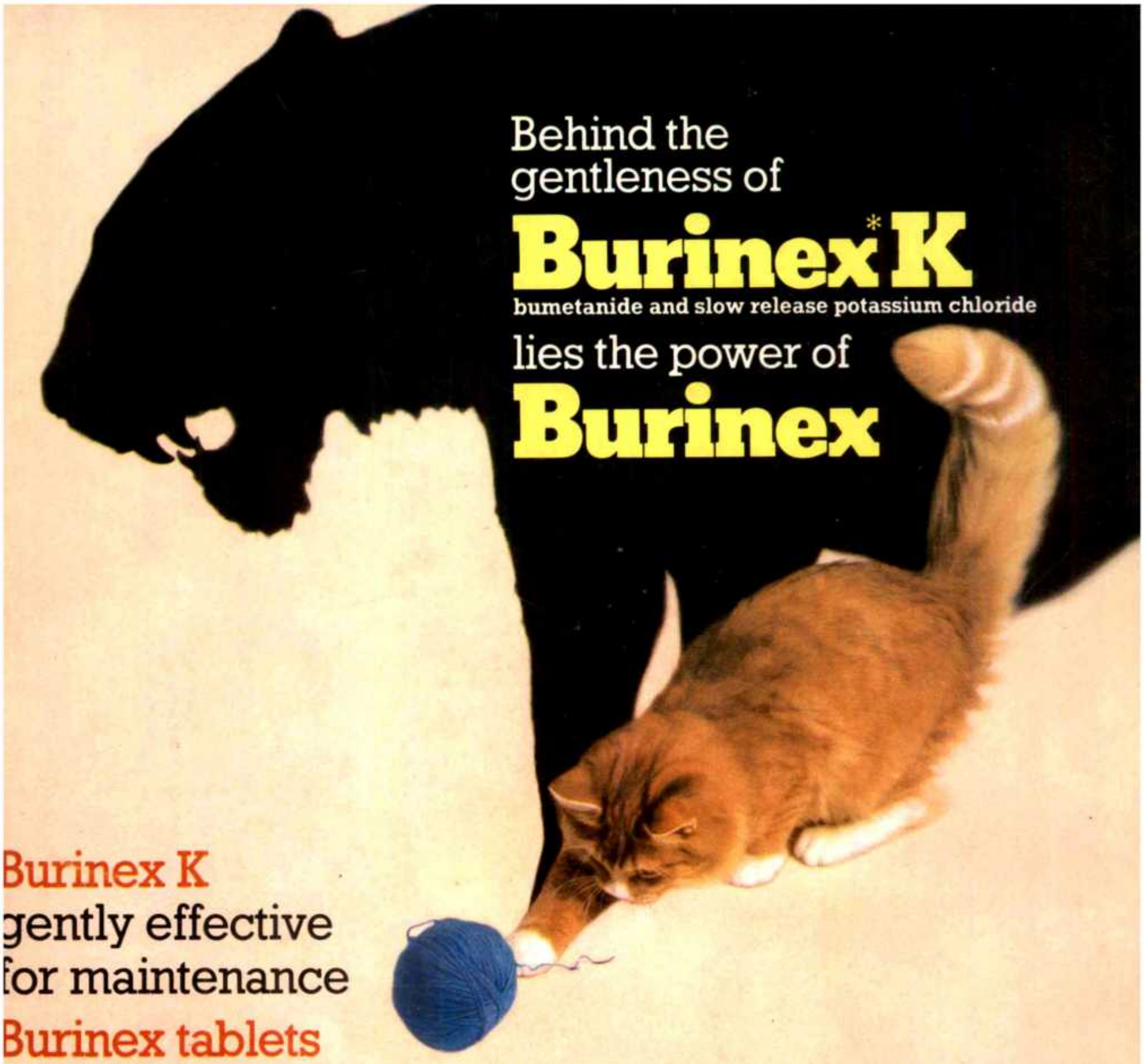
ISSN 0007-0769



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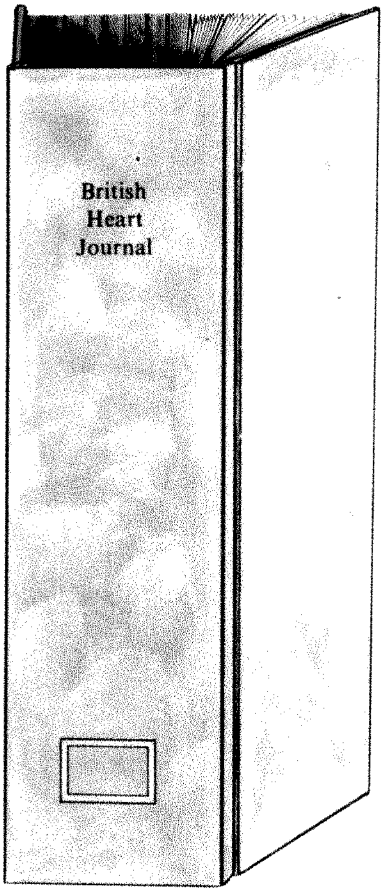

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Original Articles:

The Role of Hydralazine Therapy for Pulmonary Arterial Hypertension of Unknown Cause
Eulo Lupi-Herrera, Julio Sandoval, Mario Seoane, and David Bialostozky

EDITORIAL: Unexplained Pulmonary Hypertension
Alfred P. Fishman

The Effects of Intravenous Verapamil on Hemodynamic Status of Patients with Coronary Artery Disease Receiving Propanolol
Joshua Kieval, Edward B. Kirsten, Kenneth M. Kessler, Stephen M. Mallon, and Robert J. Myerburg

Hemodynamic Consequences of Combined Beta-adrenergic and Slow Calcium Channel Blockade in Man
Milton Packer, Jose Meller, Norma Medina, Madeline Yushak, Harry Smith, James Holt, Juan Guererro, G. Daniel Todd, Russell G. McAllister, Jr., and Richard Gorlin

EDITORIAL: Calcium-entry Blockade, Beta-adrenergic Blockade and the Reflex Control of Circulation
Stephen N. Oesterle and John S. Schroeder

Alterations in Left Ventricular Function and Coronary Hemodynamics with Captopril, Hydralazine and Prazosin in Chronic Ischemic heart Failure: A Comparative Study
Jean-Lucien Rouleau, Kanu Chatterjee, William Benge, William W. Parmley, and Beverley Hiramatsu

Attenuation of Exercise Conditioning by Beta-adrenergic Blockade
David L. Sable, H.L. Brammell, Mark W. Sheehan, Alan S. Nies, John Gerber, and Lawrence D. Horwitz

Reversal of Exercise-induced Hemodynamic and Electrocardiographic Abnormalities After Coronary Artery Bypass Surgery
Radha J. Sarma and Miguel E. Sanmarco

Analysis of Left Ventricular Pressure During Isovolumic Relaxation in Coronary Artery Disease
D.S. Thompson, C.B. Waldron, S.M. Juul, N. Naqvi, R.H. Swanton, D.J. Coltart, B.S. Jenkins, and M.M. Webb-Peploe

Effect of Large Variations in Preload on Left Ventricular Peformance Characteristics in Normal Subjects
J.V. Nixon, R. Gordon-Murray, Peter D. Leonard, Jere H. Mitchell, and C. Gunnar Blomqvist

Effect of Hydralazine on Aortic Rupture Induced by B-Aminopropionitrile in Turkeys
Charles F. Simpson and W. Jape Taylor

Patterns of Progression of Aortic Stenosis: A Longitudinal Hemodynamic Study
Stephen Wagner and Arthur Selzer

Size and Motion of the Mitral Valve Annulus in Man. II. Abnormalities in Mitral Valve Prolapse
John A. Ormiston, Pravin M. Shah, Chuwa Tei, and Maylene Wong

Echocardiographic Detection of Left Main Coronary Artery Obstruction
Lawrence D. Rink, Harvey Feigenbaum, Robert W. Godley, Arthur E. Weyman, James C. Dillon, John F. Phillips, and Jane E. Marshall

Radionuclide Measurement of Left Ventricular Volume: Comparison of Geometric and Counts-based Methods
Barry M. Massie, Barry L. Kramer, Edward W. Gertz, and Steven G. Henderson

Effect of Flow-independent Reduction of Metabolism on Regional Myocardial Clearance of ^{11}C-Palmitate
Rene A. Lerch, Steven R. Bergmann, Hans D. Ambos, Michael J. Welch, Michel M. Ter-Pogossian, and Burton E. Sobel

Contrast Enhancement of Myocardial Infarction: Dependence on Necrosis and Residual Blood Flow and Relationship to Distribution of Scintigraphic Imaging Agents
Charles B. Higgins, Phillip L. Hagen, John D. Newell, Walter S. Schmidt, and Frank H. Haigler

Characterization of Nontransmural Myocardial Infarction by Positron-emission Tomography
Edward M. Geltman, Daniel Biello, Michael J. Welch, Michel M. Ter-Pogossian, Robert Roberts, and Burton E. Sobel

Estimation of Acute Myocardial Infarct Size in Man by serum CK-MB Measurements
Peer Grande, Birgit Fischer Hansen, Claus Christiansen, and Jørgen Naestoft

Intravenous Hyaluronidase Therapy for Myocardial Infarction in Man: Double-blind Trial to Assess Infarct Size Limitation
John A. Cairns, Douglas A. Holder, Paul Tanser, and Eleftheria Missirlis

Intravenous Isosorbide Dinitrate in Patients with Refractory Pump Failure and Acute Myocardial Infarction
Babeth Rabinowitz, Israel Tamari, Ella Elazar, and Henry N. Neufeld

Pathophysiology of Chest Pain in Patients with Cardiomyopathies and Normal Coronary Arteries
André Pasternac, Jacques Noble, Yves Streulens, Robert Elie, Claudia Henschke, and Martial G. Bourassa

Factors in Predicting Blood Pressure Change
David Sparrow, Arthur J. Garvey, Bernard Rosner, and H. Emerson Thomas Jr.

A Comparative Study of Serum Lipids Between Belgium and Korea
H. Kestellot, C.S. Lee, H.M. Park, C. Kegels, J. Geboers, J.H. Claes, and J.V. Joossens

Termination of Ventricular Tachycardia with Ventricular Stimulation: Salutary Effect of Increased Current Strength
Harvey L. Waxman, Michael E. Cain, Allan M. Greenspan, and Mark E. Josephson

Case Reports:

Pulmonary Atresia with Intact Ventricular Septum and Ventriculocoronary Communications: Surgical Significance
William N. O'Connor, Carol M. Cottrill, Gregory L. Johnson, Jacqueline A. Noonan, and Edward P. Todd

Bilateral Coronary Artery-Pulmonary Artery Fistulas. Report of Five Cases and Review of the Literature
Donald S. Baim, Howard Kline, and James F. Silverman

Detection of Mitral Ring Abscess by Two-dimensional Echocardiography
Kenji Nakamura, Shin Suzuki, Gengi Satomi, Hisae Hayashi, and Koshichiro Hirosawa

Pneumonitis and Pulmonary Fibrosis Associated with Amiodarone Treatment: A Possible Complication of a New Antiarrhythmic Drug
Samuel M. Sobol and Louis Rakita

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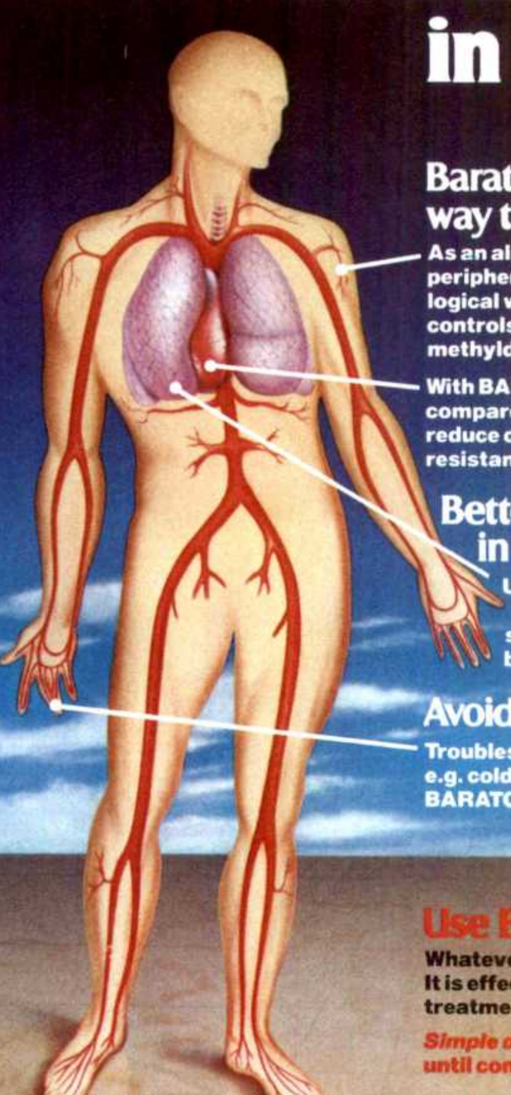

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22/34/1. 50mg tablets PL0011/0058. PA 22/34/2. **References**: 1 Marks, P. Data on file. 2 Carballo, R. (1977) *in Arterial Hypertension*. Ed Velasco M., Excerpta Medica, p129. 3 Archibald, J. L. (1980) *Pharmacology of Anti-hypertensive drugs*. Ed. Scriabine, A., Raven Press, N.Y. 161. 4 Coltart, J. (1981) *Brit. J. Clin. Pharmacol.*, **12**, 49. 5 Zacharias, F. J. (1981) *Brit. J. Clin. Pharmacol.*, **12**, 105. 6 Fitzgerald, M. V. J. (1981) *Brit. J. Clin. Pharmacol.*,
12, 117. 7 Johnson, E. S. (1981) *Brit. J. Clin. Pharmacol.*, **12**, 131. Further information is available on request. **Wyeth Laboratories**, John Wyeth & Brother Ltd., Taplow, Maidenhead, Berks. *Trade marks BAR 1/03/282

Notices

Br Heart J 1982; **48:** 308

The First World Congress on Cardiovascular Pharmacotherapy will take place in Geneva, Switzerland from 11 to 15 April 1983. Inquiries to Interconférence, 12 Ave. des Amazones, 1224 Chêne-Bourgeries, Geneva, Switzerland.

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext 263) to whom they should be returned.

British Cardiac Society

The Autumn Meeting 1982 will take place on 6 and 7 December. The closing date for receipt of abstracts was 11 August.

The Annual General Meeting for 1983 will take place in Bristol on 12 and 13 April, and the closing date for abstracts will be 4 January 1983.

The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts will be 28 July 1983.

Correspondence

Br Heart J 1982; **48**: 307

Echocardiographic diagnosis of isolated pulmonary valve endocarditis

Sir,
In the case report (*British Heart Journal* 1982, **47**: 298–300), the authors confirm the value of echocardiography in the diagnosis of pulmonary valve vegetations. They do not comment on the echocardiographic assessment of the pattern of leaflet motion. We have demonstrated the value of the cross-sectional echocardiogram in showing the flail nature of the leaflets in a further patient with pulmonary valve vegetations,[1] and it would be interesting to know if the authors have any information in their case. The two dimensional approach is more likely to show details of the size and shape of the vegetations and the leaflet motion than M-mode echocardiograms. Our patient has now been reviewed over a two year period, and there have been no changes in the echocardiographic features, and no deterioration in his clinical condition. Surgery does not seem to be required in such cases if the initial infection can be successfully treated with antibiotics.

A K Brown, V Anderson, C L Gillgren,
Cardiac Investigations Department,
Royal Lancaster Infirmary,
Lancaster.

Reference

Anderson V, Gillgren CL, Brown AK. Pulmonary valve vegetations and flail leaflet detected by cross-sectional echocardiography in infective endocarditis. *Eur Heart J* 1981; 2: 519–23.

Br Heart J 1982; **48**: 306

Oxford pacemaker infection trial

Sir,

We read with interest the Oxford pacemaker infection trial. This came at a time when we in Leeds were conducting a similar prospective investigation into the effect of antibiotics on pacemaker infections. Our trial consisted of 67 patients who had satisfied the exclusion criteria. The latter were essentially similar to those in the Oxford trial but also excluded diabetics from randomisation as we felt there was enough evidence showing that these patients have an increased predisposition to staphylococcal infections. Of the 67 patients in the trial, there was one infection in the treated and one in the untreated group.

We think that the Oxford data are convincing. For those still doubting this evidence, antibiotic prophylaxis must remain mandatory for the at-risk patients undergoing early re-exploration of their generator pockets. We also consider diabetics to be at increased risk of staphylococcal infection and would always advocate the use of antibiotics in this group.

M A Young,
Department of Cardiovascular Medicine,
East Birmingham Hospital,
Bordesley Green East,
Birmingham B9 5ST.

D R Smith,
Leeds General Infirmary,
Great George Street,
Leeds.

2 Watkins WD, Peterson MB, Crone RK, Shannon DC, Levine L. Prostacyclin and prostaglandin E_1 for severe idiopathic pulmonary artery hypertension (letter). *Lancet* 1980; i: 1083.
3 Szczeklik J, Dubiel JS, Mysik M, Pyzik Z, Krol R, Horzela T. Effects of prostaglandin E_1 on pulmonary circulation in patients with pulmonary hypertension. *Br Heart J* 1978; **40**: 1397–401.
4 Szczeklik J, Szczeklik A, Nizankowski R. Prostacyclin for pulmonary hypertension (letter). *Lancet* 1980; ii: 1076.
5 Bergström S, Dunér H, Von Euler US, Pernow B, Sjovall J. Observations on the effects of infusion of Prostaglandin E in man. *Acta Physiol Scand* 1959; **45**: 145–51.
6 Carlson LA, Olsson AG. Intravenous Prostaglandin E_1 in severe peripheral vascular disease (letter). *Lancet* 1976; ii: 810.

This letter was shown to Dr Ikram who replies as follows.

Sir,

The authors conclude that PGE_1 infusion in their case produced no reduction in pulmonary arterial pressure and an increase in pulmonary resistance. Unfortunately their data are complicated by the prior administration of diazoxide and though they claim that the haemodynamic status had returned to baseline levels, this is clearly not the case at the start of the PGE_1 infusion. If the haemodynamic measurements immediately before the PGE_1 at 32 ng level are taken as control, then there is a small fall in systemic and pulmonary vascular resistance and a rise in cardiac output with consequently no change in pulmonary pressure. PGE_1 is not as potent a vasodilator as PGI_2 (prostacyclin) and there are patients who respond minimally even to this, the most potent naturally occurring pulmonary vasodilator.

The general experience with all vasodilator therapy in pulmonary hypertension is that responses tend to be variable and unpredictable. The fact that the vasculature was more responsive to vasodilators previously suggests the development of obstructive changes which would not be influenced by PGE_1. The authors talk about lack of "benefit". It is difficult to assess or even define what constitutes benefit in this situation. A fall in pulmonary pressure would be desirable but frequently does not occur because of increased flow. The best estimate would be regression of right ventricular hypertrophy but this is not possible in an acute study. Improvement in right ventricular function assessed by pressure and radionuclide methods would help in assessing beneficial action but was not performed.

I would certainly endorse the authors' comments that "the effect of PGE_1 in the pulmonary circulation in man remains to be clarified" especially in patients with pulmonary vascular disease.

Hamid Ikram,
Department of Cardiology,
The Princess Margaret Hospital,
Cashmere Road,
Christchurch 2,
New Zealand.

In both the injected and uninjected uninflated tissue, pulmonary vascular structure was analysed using quantitative morphometric techniques.[6-8] In each case, the percentage wall thickness of both arteries and veins was determined. The vessels were grouped according to their external diameter and the mean percentage wall thickness was calculated for each size range. For each case, percentage wall thickness was determined in each lobe separately. The mean external diameter and the proportion of non-muscular, partially muscular, or entirely muscularised arteries accompanying each type of peripheral airway (terminal bronchioli, respiratory broncholi, and alveolar ducts) were assessed for each lobe. The results in each lobe and, where possible, each lung were compared using Student's t test.

In order to estimate the number of intra-acinar* arteries and veins the ratio of alveoli to arteries and alveoli to veins was determined in the injected tissue of cases 4 and 5.

On the fixed specimens the lumen diameter of the extrapulmonary veins was measured in all except case 4. In four cases of infradiaphragmatic total anomalous pulmonary venous return the lumen diameter of the descending vertical vein was also measured. Fig. 1 indicates those extrapulmonary veins and regions of the descending vertical vein selected for histological examination. The descending vertical vein was thick walled for a distance of 1·5 cm proximal to its entering the porta hepatis in case 2, and the lumen was occluded in this region in case 6. In both cases, a serial reconstruction was made of this part of the descending vertical vein.

All histological sections of lung and venous tissue were 4 μm thick and stained with haematoxylin and eosin and with Miller's elastic stain counterstained with van Gieson's stain. The serial sections were all stained with Miller's elastic stain.

Results

On microscopical examination of the lung tissue, in all cases the alveoli appeared normal, were mature, and not saccular. The lymphatic channels were considerably dilated in all sections of lung tissue examined. In the injected specimens, the two postmortem arteriograms and one lobar venogram showed a normal branching pattern and no stenoses.

INTRAPULMONARY ARTERIES

In all cases the media of the intrapulmonary arteries appeared thicker than normal. In each case, in both injected and uninjected tissue, mean percentage arterial medial thickness in arteries of all sizes was significantly greater than is normal at 5 hours of age in all parts of the lung examined (Fig. 2 and 3). The increase in muscularity was similar in different parts of

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*An acinus is all lung tissue distal to a terminal bronchiolus.

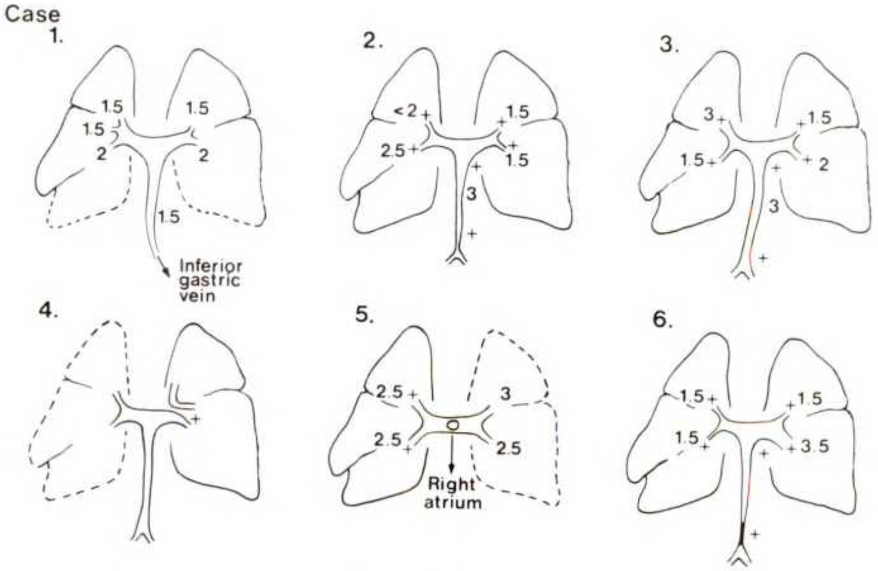

Fig. 1 *Diagram to show the type of total anomalous pulmonary venous return and the lumen diameter of the extrapulmonary veins and descending vertical vein (mm). The lobes of lung examined histologically are indicated by a continuous outline to the lung, and those lobes not examined histologically are indicated by an interrupted line. The extrapulmonary and descending vertical veins examined histologically are shown by a +.*

the same lung and in the two lungs of the same case where the tissue was available for such a comparison to be made. Microscopical examination of the lung tissue from all cases and the quantitative studies on the injected lung specimens of cases 4 and 5 showed that muscle was present in smaller and more peripheral arteries than is normal (Fig. 3 and 4).

Intimal proliferation was not seen.

The mean external diameter of arteries accompanying peripheral airways in both injected and uninjected tissue was within normal limits for age. Within each case there was no significant regional variation in intra-acinar arterial size. In all cases the number of intra-acinar arteries appeared normal on general microscopical examination. More precisely, the ratio of alveoli to arteries was normal in the injected tissue of cases 4 and 5, being 10·4 and 9·4, respectively.

INTRAPULMONARY VEINS

Like the arteries, the intrapulmonary veins seen in all the sections of lung tissue examined microscopically from all six cases showed an increase in wall thickness of both pre- and intra-acinar vessels. The intra-acinar veins had a thickened media and a well-defined external elastic lamina, and resembled arteries (Fig. 5). The media of the large preacinar veins consisted of thick continuous elastic fibres separated by an increased amount of smooth muscle (Fig. 6). A thick adventitia was composed of densely arranged collagen fibres.

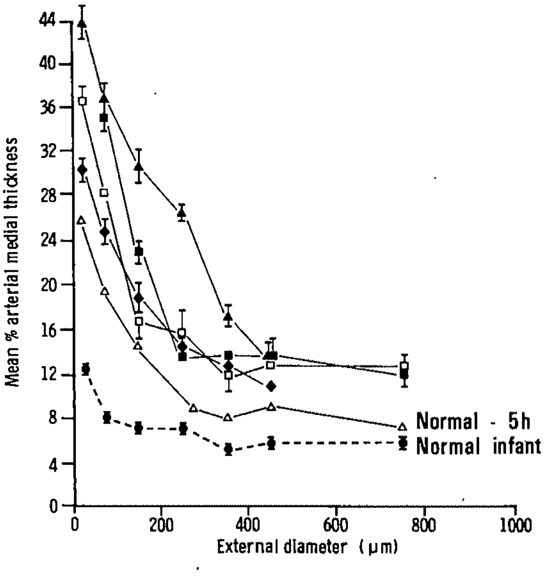

Fig. 2 *Uninjected lung tissue. Mean percentage arterial medial thickness related to external diameter (µm), showing the increase in muscularity in four cases of total anomalous pulmonary venous return as compared with the normal at 5 hours and in older infants. Case 1* □—□; *case 2* ▲—▲; *case 3* ■—■; *case 6* ♦—♦; *SE*I.

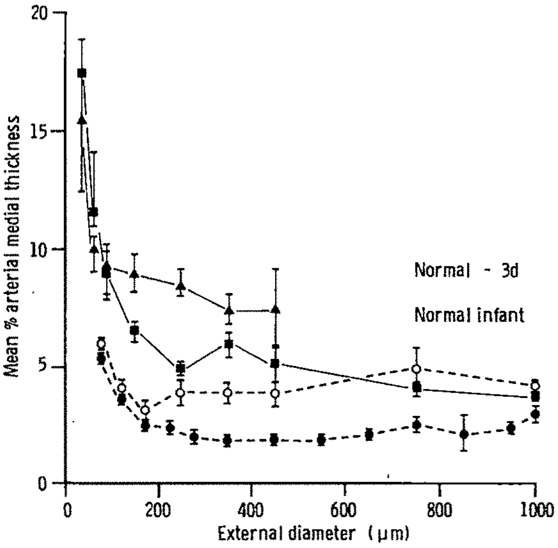

Fig. 3 *Injected lung tissue. Mean percentage arterial medial thickness related to external diameter (µm) showing the increase in muscularity in cases 4 and 5 as compared with the normal at 3 days and in older children.*
Case 4 ▲—▲; *case 5* ■—■; *SE*I.

Like the arteries, intimal proliferation was not found in the intra-acinar veins in any of the cases. By contrast, the preacinar intrapulmonary veins showed intimal proliferation in two cases, being found in both lower lobes of case 3, and in the right upper and lower lobe of case 5.

Mean percentage vein wall thickness was significantly greater than normal in all cases, using uninjected tissue in five cases and injected tissue in case 5 (Fig. 7). The normal tissue used for comparison included that of stillborn fetuses aged 36 and 38 weeks and full-term infants up to 6 hours of age. In normal infants mean percentage vein wall thickness does not change significantly after birth.[9] At 1 to 6 days (the age at which the children in the study group died) muscularity would certainly not be greater than in these controls. In the cases of total anomalous pulmonary venous return analysis of the tissue available showed no significant difference in vein wall muscularity between different lobes or between different lungs of the same case.

Accurate counts of the number of small intrapulmonary veins related to the number of alveoli were possible only in the injected specimen of case 5, where the alveolar to vein ratio was normal at 4:1. The

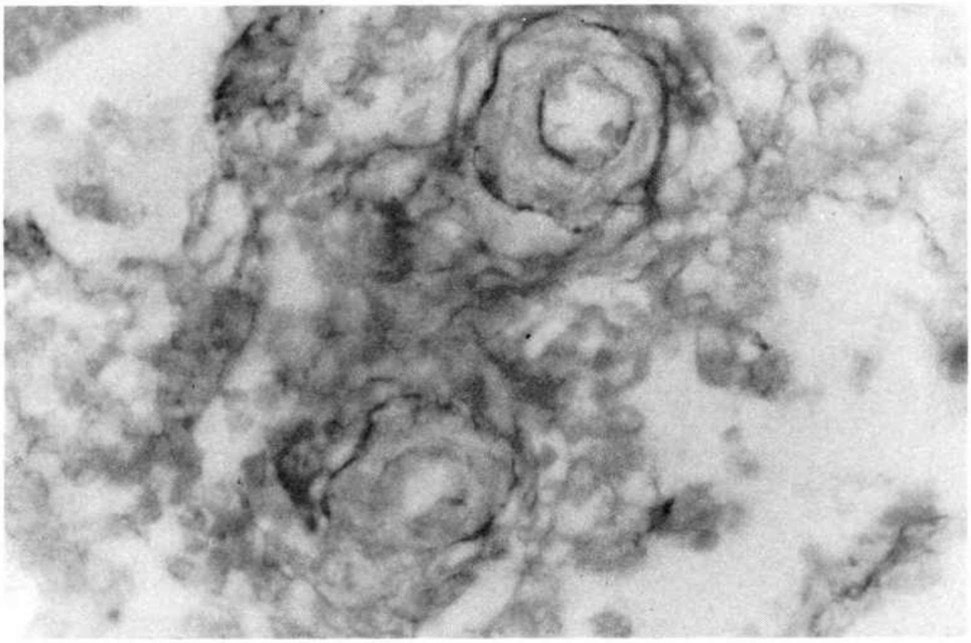

Fig. 4 *Photomicrograph of thick walled muscular alveolar wall arteries. (Original magnification ×540.)*

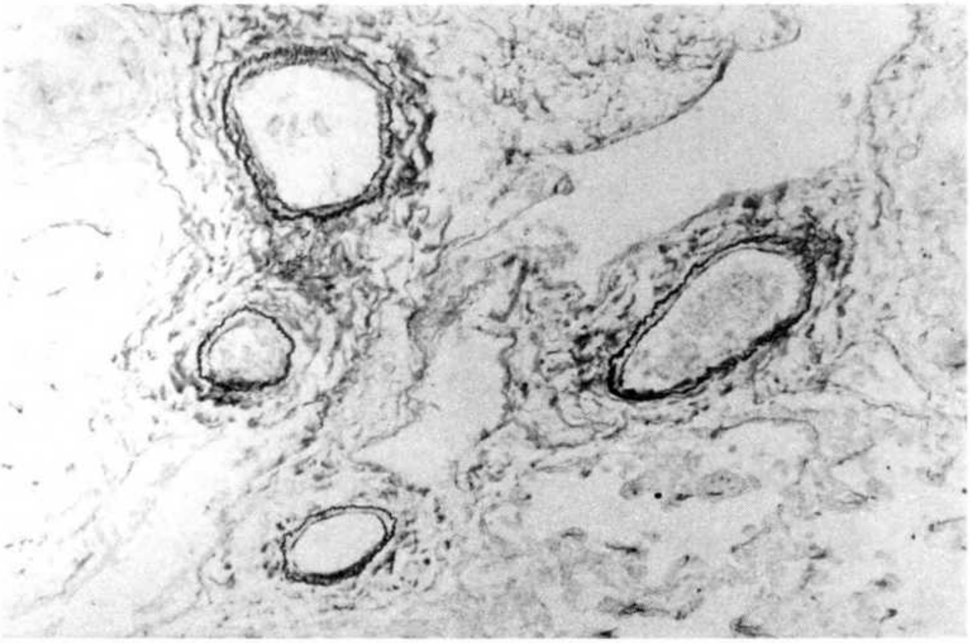

Fig. 5 *Photomicrograph of thick walled muscular small pulmonary veins which resemble arteries. (Original magnification ×367.)*

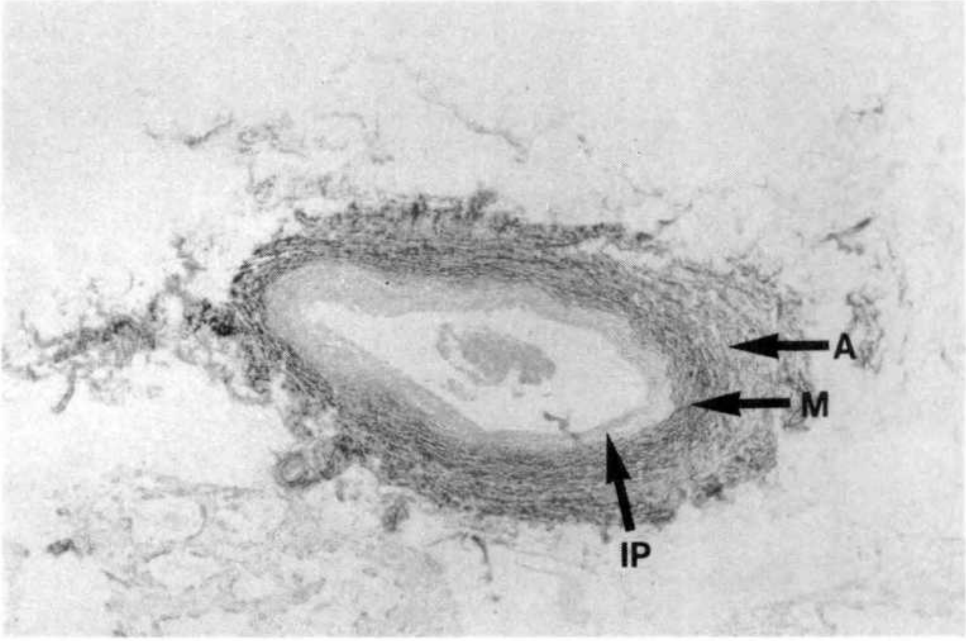

Fig. 6 *Photomicrograph of a large preacinar pulmonary vein with a thickened media (M) and adventitia (A) and intimal proliferation (IP). (Original magnification ×38).*

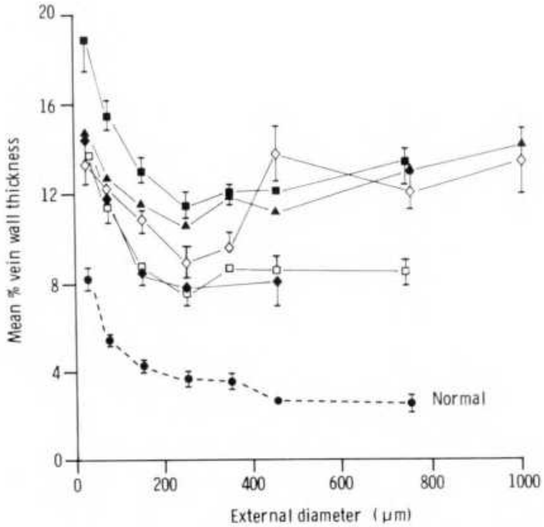

Fig. 7 *Mean percentage vein wall thickness in uninjected tissue, related to external diameter (μm), showing an increase in vein wall thickness in five cases of total anomalous pulmonary venous return as compared with the normal of similar age.*
Case 1 ■—■; case 2 □—□; case 3 ◇—◇; case 4 ♦—♦; case 6 ▲—▲; SE I.

right upper lobe venogram in case 5 showed a normal lumen diameter of 1 to 1·8 mm in the veins situated midway between the hilum and pleural surface.

PULMONARY VEIN–BRONCHIAL VEIN ANASTOMOSES

Connections between dilated thick walled pulmonary veins and thin walled bronchial veins were identified more readily than in the normal lung in both uninjected and injected tissue. In addition, injecting the pulmonary veins filled enlarged bronchial veins with injection material more frequently than is normal (Fig. 8).

EXTRAPULMONARY VEINS

In the normal fixed specimen the lumen diameter of the undistended pulmonary veins during the first week of life is 2 to 3 mm. Histologically, the wall has a thin media and an adventitia containing a layer of myocardial fibres (Fig. 9a). In the five cases of total anomalous pulmonary venous return in which the extrapulmonary veins were examined the veins varied in size within and between cases, were generally smaller than normal, and only in case 5 were all the veins at least 2 mm in diameter (Fig. 1). Macroscopically, the wall was abnormally thick in the veins of cases 2, 3, and 6. Microscopically, the thick extrapulmonary veins in these three cases and in case 5 showed similar structural features (Fig. 9b). Within the wall three or four thick continuous elastic fibres separated by muscle cells could be distinguished and this layer resembled the media of a normal extrapulmonary vein. Occasionally, this layer was immediately beneath the intima, but more commonly it lay beneath several layers of elastic fibres with interspersed muscle cells and collagen (Fig. 9b). Because the adventitia contained long, thick elastic fibres, the walls of all the extrapulmonary veins examined contained 12 to 20 layers of elastic fibres. In cases 2, 3, and 6 the extrapulmonary veins contained eccentric areas of amorphous intimal tissue (Fig. 9b). No myocardial muscle fibres were seen in any of the extrapulmonary veins.

DESCENDING VERTICAL VEIN

In four of the five children with infradiaphragmatic total anomalous pulmonary venous return, the descending vertical vein was patent throughout except in case 6 when it was occluded for a distance of 4 mm immediately proximal to its connection with the portal system. In all except case 1, the descending vertical vein had a diameter of 3 to 3·5 mm throughout all or most of its length. In case 1 it measured only 1 to 2 mm in diameter. The microscopical features were similar in

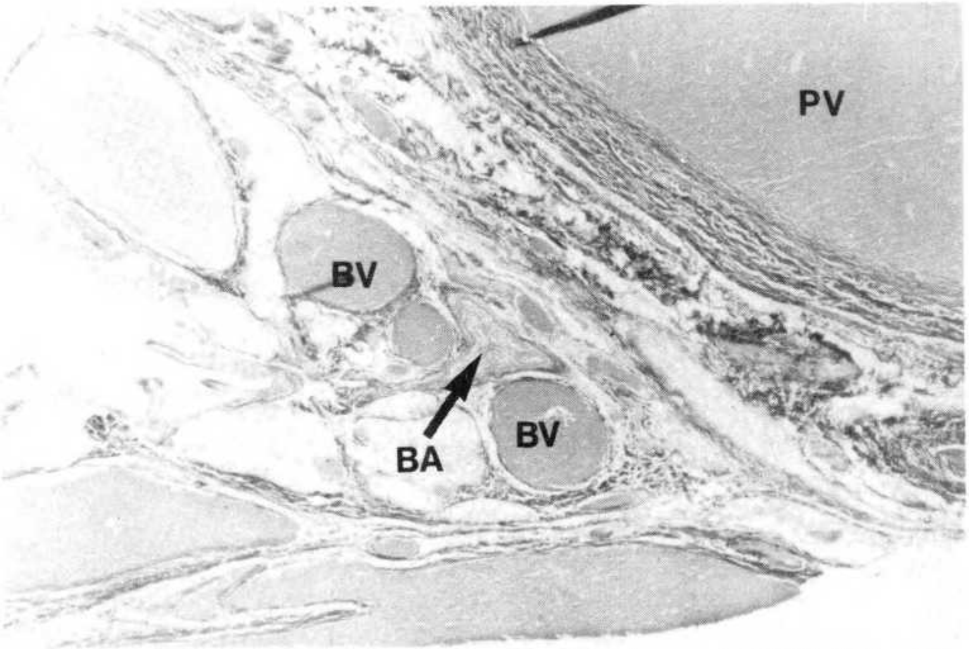

Fig. 8 *Photomicrograph of injected lung tissue in case 4. Injection of the pulmonary veins (PV) filled the bronchial veins (BV). BA, bronchial artery. (Original magnification ×38.)*

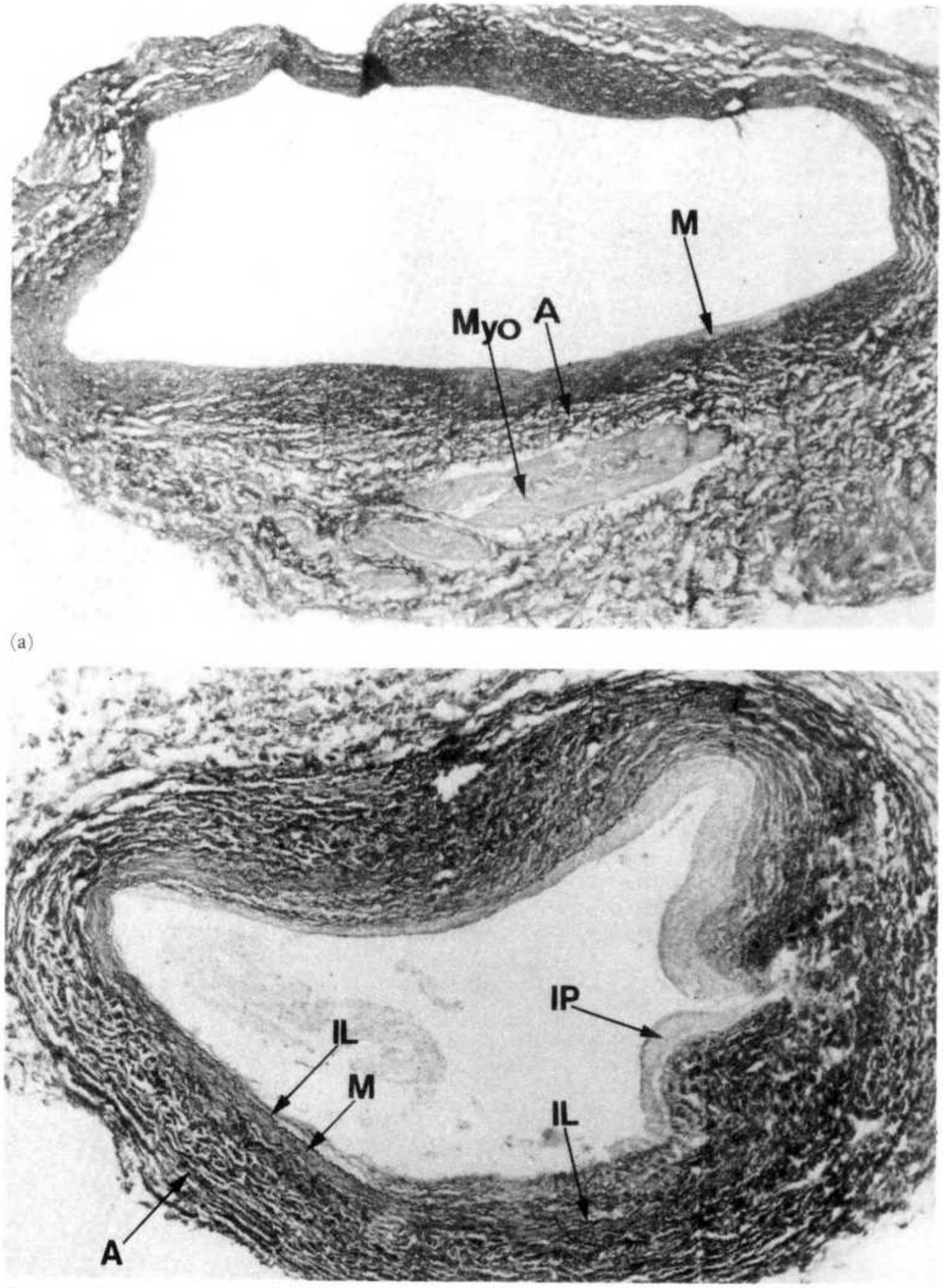

Fig. 9 (a) *Photomicrograph of the wall of an extrapulmonary vein from a normal lung at the age of 3 days. Muscle layer (M) is thin. Myocardial fibres (Myo) are present in the adventitia (A). (Original magnification ×38.)* (b) *Photomicrograph of the left lower lobe pulmonary vein in case 3. Internal elastic lamina (IL) demarcates the muscle layer (M) from the intimal proliferation (IP). The adventitia (A) is abnormally thick and dense and contains much elastin. (Original magnification ×38.)*

all three specimens examined histologically. Beneath the endothelium lay a thin layer composed of three to four long unfragmented elastic fibres interspersed with smooth muscle cells. A thick adventitia was composed of dense collagen, and long continuous elastic fibres were concentrated in the outer half of the wall. No myocardial fibres were present. In case 2 a serial reconstruction showed that as the vein approached the diaphragm the wall became thicker, and small eccentric unobtrusive mounds of intimal tissue projected into the lumen. In case 6 these changes were more pronounced until the descending vertical vein became occluded with collagen fibres (Fig. 10).

In all four children who had undergone a surgical repair the anastomosis between the left atrium and common pulmonary vein was wide and measured 7 to 8 mm in diameter in the fixed specimen.

Summary of pathological findings

Of the five patients with infradiaphragmatic total anomalous pulmonary venous return, the descending vertical vein was patent in four, the extrapulmonary veins were generally smaller than normal in all, and the vein wall was abnormally thick and showed intimal proliferation in three cases. In the one case of total anomalous pulmonary venous return to the right atrium the extrapulmonary veins were normal in size and thickness, though the histological features were similar to those in cases of the infradiaphragmatic type of drainage. The extrapulmonary veins were composed of an increased amount of collagen and elastin, without myocardial fibres in the adventitia.

Pulmonary arterial medial thickness was increased, and muscle was present in smaller more peripheral arteries than is normal for age. The intra-acinar arteries were normal in size and appeared to be normal in number. In all cases the mean percentage vein wall thickness was increased in pre- and intra-acinar veins. Intimal proliferation occurred in the large pre-acinar veins of two of the six cases, though in no case was it present in all parts of the lung examined. The number of intra-acinar veins appeared normal. Anastomoses between small pulmonary and bronchial veins present in the normal lung were prominent in uninjected material, and in the one injected specimen the pulmonary veins frequently filled the bronchial veins also. Within the group of six cases, there was no relation between the amount of pulmonary arterial or venous muscularity and age.

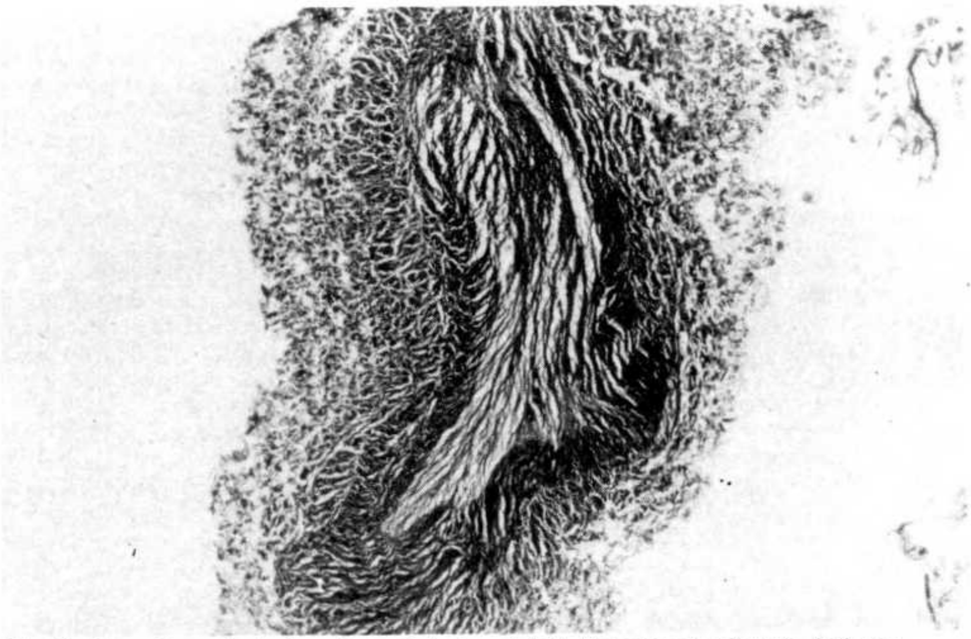

Fig. 10 *Photomicrograph of a descending vertical vein occluded by fibrous tissue just above the diaphragm. (Original magnification ×38.)*

Discussion

In six patients dying with obstructed total anomalous pulmonary venous return during the first six days of life, an increase in the muscularity of the intrapulmonary arteries and veins indicates that obstruction to pulmonary venous outflow was present before birth. The deposition of increased amounts of smooth muscle, elastin, and collagen in both extra- and intrapulmonary veins, and the narrowing or even occlusion of the descending vertical vein by collagen rather than by amorphous acellular material suggest that obstruction to pulmonary venous return had been present for a considerable time before birth. Patients with the infradiaphragmatic type of total anomalous pulmonary venous return are usually considered to have obstruction to pulmonary venous return because of the length and relatively small cross-sectional area of the anomalous venous pathway and the resistance to blood flow through the hepatic sinusoids when the ductus venosus is closed. In the present study, the size of the descending vertical vein appeared to obstruct flow in three of the five cases with infradiaphragmatic total anomalous pulmonary venous return. In the one patient in whom the pulmonary veins drained anomalously to the right atrium, an anatomical site of obstruction was not identified. The structural change within the lungs and the severity of the pulmonary hypertension were, however, as severe in all three patients without demonstrated anatomical obstruction as in those with obstruction.

Despite partial or even total obstruction to pulmonary venous drainage in all six cases the lungs continued to grow in utero and after birth sustained life for up to six days. It has been suggested that in the presence of pulmonary venous hypertension the anastomotic channels between pulmonary and bronchial veins present in the normal lung widen to allow blood to flow from the pulmonary veins to the pulmonary branches of the bronchial veins and thence into the azygos system and superior vena cava.[10 11] In the arterial circulation, anastomoses between the pulmonary and systemic circulations occur more frequently in the newborn than in the older lung[12] and the same may be true of the venous systems. In some patients there was a considerable variation in the lumen diameter of the extrapulmonary veins, but there was no significant regional variation in either arterial or venous muscularity in the cases studied. Ferencz and Dammann[13] found arterial medial hypertrophy in both lungs in the presence of unilateral pulmonary venous obstruction. Possibly the wealth of venous anastomoses in the lung and the pleurohilar network of bronchial veins help to reduce the effect of regional differences in the severity of obstruction to pulmonary venous outflow. The pronounced dilatation of the lymphatic channels in all cases in the present series attests to the increased drainage of fluid from the lung by this route.

In the present study intrapulmonary arterial and venous muscularity was increased. Using the same techniques of quantitative morphometric analysis, a similar increase in muscularity has been found in a slightly older group of children dying with obstructed total anomalous pulmonary venous return during the first three months of life.[6] The structural changes in the veins were more severe in the present study, particularly in the preacinar veins which were very thick walled and showed intimal proliferation in two cases. Most of the structural changes present in both arteries and veins were, however, potentially reversible in both series of cases. Newfeld *et al.*[5] studied an older group of patients aged 5 days to 12 years (median 3 months), and reported more advanced pulmonary vascular disease. In that series, 12 of the 13 children aged 1 month or less had arterial cellular intimal proliferation and four had occlusive intimal fibrosis, though these changes were not necessarily found in more than a few of the arteries examined. The present study indicates that children with total anomalous pulmonary venous return who present to the cardiologist during the first days of life may have been born with significant pulmonary vascular disease. These findings help to explain the sudden and unexplained increases in pulmonary arterial pressure and resistance which occur in some young infants immediately after repair of the anomaly.[14] The increase in muscularity probably encourages both arteries and veins to vasoconstrict in response to hypoxia and acidosis, making the lung extremely vulnerable despite the absence of severe occlusive intimal change in young infants. The administration of pulmonary vasodilator substances such as tolazoline[14] or dopamine has been found to lower the pulmonary vascular resistance on such occasions.

The type of pathological change found in the arterial walls of young infants with total anomalous pulmonary venous return is generally considered to be reversible. In addition, the intra-acinar arteries are generally normal in size and number. In practice, patients with total anomalous pulmonary venous return who undergo repair and survive have a normal pulmonary vascular resistance unless pulmonary venous obstruction is present for any reason.[15 16]

Several published follow-up studies on patients with total anomalous pulmonary venous return who had undergone a satisfactory surgical repair in early infancy include one or more patients who developed stenosis of at least one extrapulmonary vein.[1 2 17 18] The present study includes several instances of small thick walled extrapulmonary veins, sometimes showing intimal fibrosis. The lumen of the vessels was narrowed because the vessel was intrinsically small. There was no instance of narrowing by external compression or by a localised stricture or a diaphragm. The normal pulmonary vein is thin walled and readily distensible. Abnormally thick walled, small veins may fail to grow normally as the cardiac output increases with growth, encouraging further intimal proliferation and fibrosis, to give an appearance similar to that described by Friedli *et al.*,[18] Katz *et al.*,[2] and Whight *et al.*[15] in their cases. Haemodynamic studies on a group of apparently healthy survivors suggested that relative narrowing of the pulmonary veins might occur frequently, but was usually "unimportant and non-progressive".[15]

Pulmonary venous stenosis has occurred after repair of the total anomalous pulmonary venous return to the coronary sinus[2 15 19 20] and to the liver.[1 15 17] Babies with infradiaphragmatic total anomalous pulmonary venous return may, however, be particularly disposed to develop pulmonary vein stenosis. In the majority of these babies, pulmonary venous return is obstructed. Narrowing of the common pulmonary vein, as seen in three cases in the present series, may help explain the increased wall thickness of the extrapulmonary veins at birth in such children, predisposing them to further occlusive pulmonary venous change after repair. In two children with infradiaphragmatic total anomalous pulmonary venous return who developed postoperative pulmonary vein stenosis, patch angioplasty was successful initially, but the veins subsequently became restenosed.[1] It may perhaps be more difficult to achieve satisfactory permanent relief of pulmonary vein stenosis in patients with total anomalous pulmonary venous return because the whole vein is small, rather than there being a localised constriction.

In a recent surgical series patients with the infradiaphragmatic type of total anomalous pulmonary venous return had a higher mortality, both early and late, than did those with other types of total anomalous pulmonary venous return.[1] The present study also suggests that this group of patients is particularly vulnerable. Five of the six consecutive specimens referred for study from children dying with obstructed total anomalous pulmonary venous return during the first week of life showed the infradiaphragmatic type of pulmonary venous return. Both the intrapulmonary vessels and extrapulmonary veins showed structural abnormalities likely to increase the operative risk and predispose such patients to the development of pulmonary vein stenosis after a technically successful surgical repair.

The author wishes to thank the physicians, surgeons, and pathologists of the Brompton Hospital, Guy's Hospital, and the Hammersmith Hospital for permission to study their cases.

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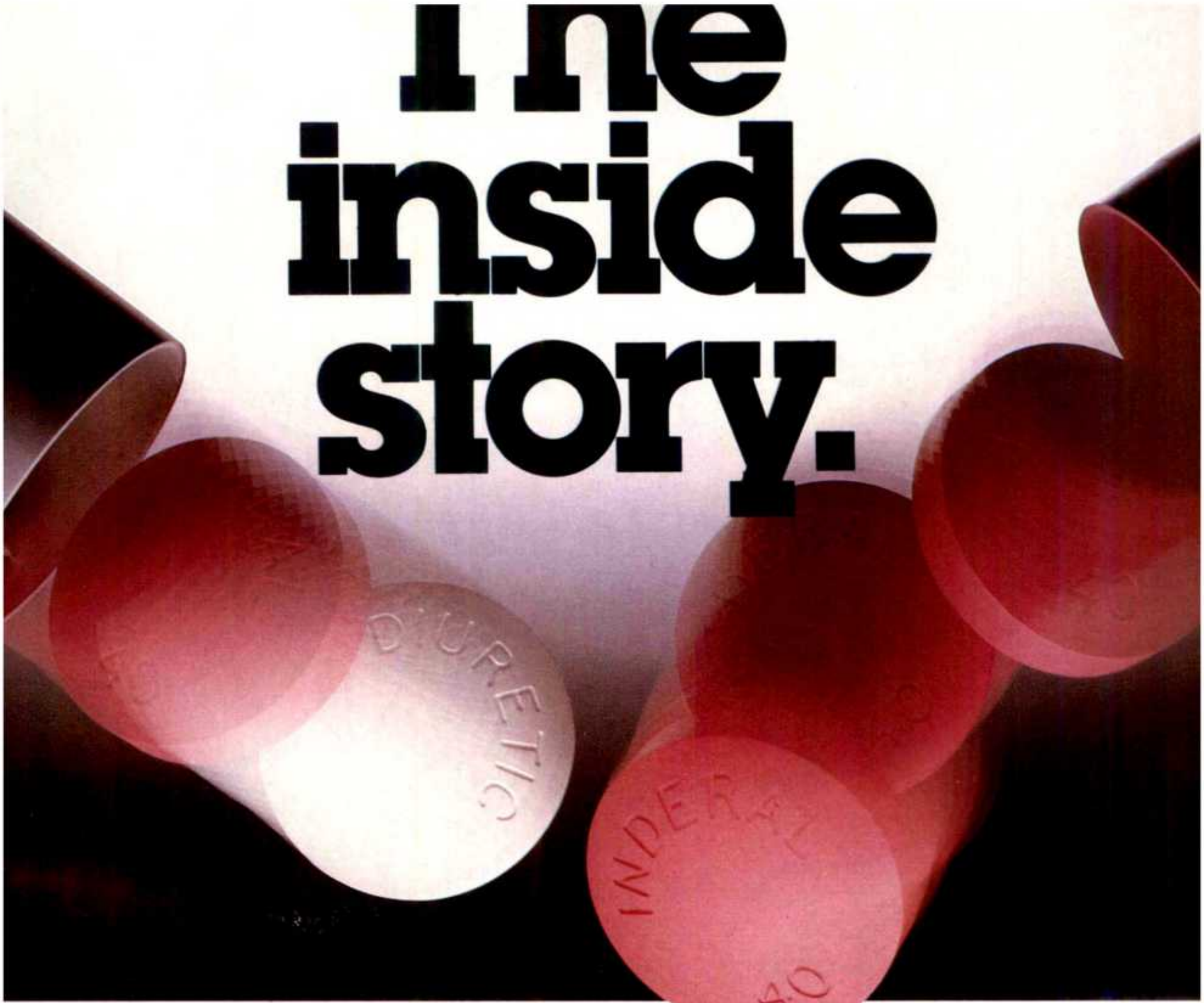

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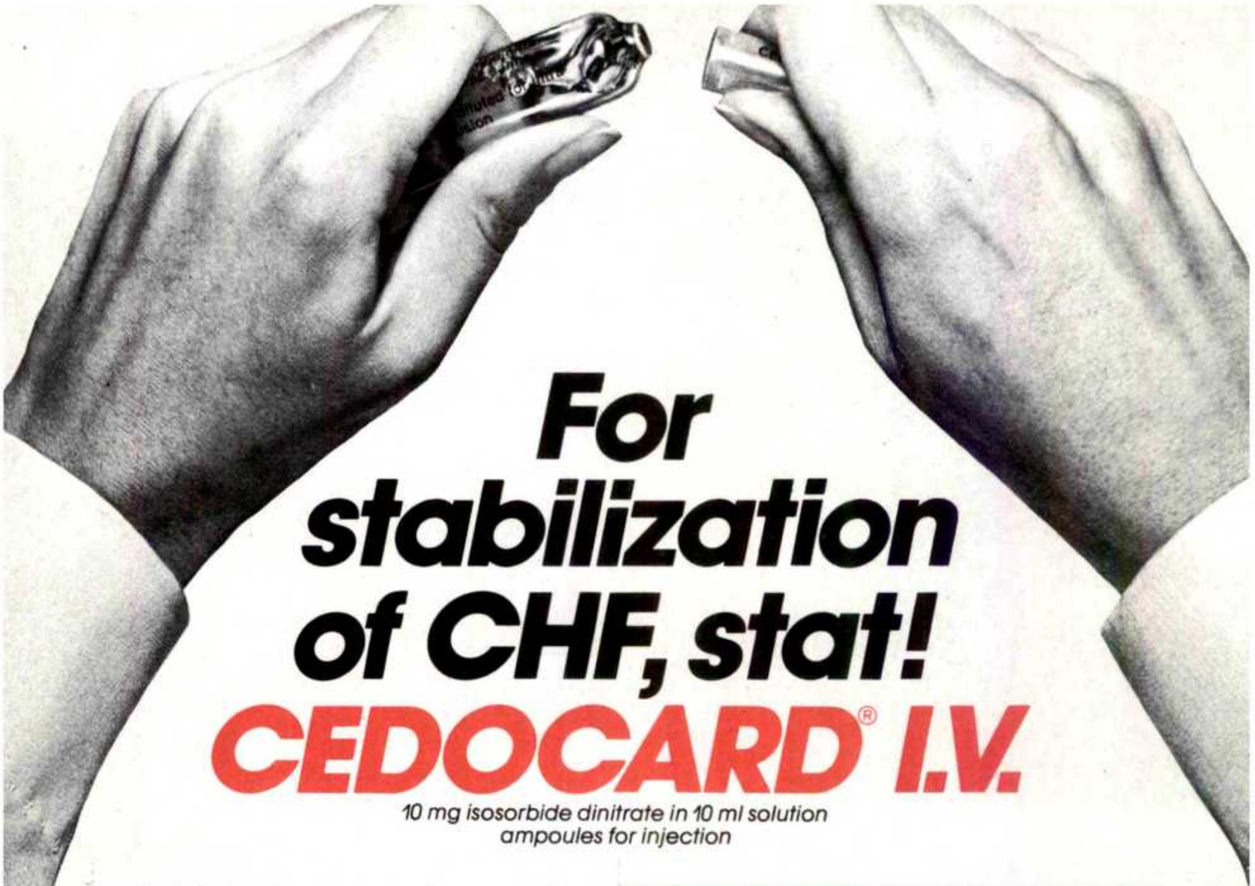

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Computer analysis of cardiac contractility variables obtained by M-mode echocardiography in normal newborns

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SUMMARY There are few echocardiographic studies which examine ventricular cavity and wall dimensions as well as ventricular function in normal newborn infants. We investigated the M-mode echocardiograms of 60 normal newborn infants aged 3 to 6 days using computer analysis. Using the same method, we examined in addition left ventricular cavity dimensions and contractility variables of 15 healthy newborn infants sequentially during the first hour of life. The left and right ventricular diameters, their systolic shortening fraction and maximal rate of change, as well as the thickness of the interventricular septum and the left ventricular posterior wall were found to be comparable to previously published values. In addition, we found that the left ventricular end-diastolic diameter and the systolic shortening fraction of the left ventricular diameter increase significantly during the first hour of life. This increase is probably because of the postnatal increase in left ventricular volume and pressure work.

M-mode echocardiography is useful for studying normal and pathological cardiac anatomy in newborn infants. In addition, it provides information on the size and function of the left ventricle and, within limits, the right ventricle. In order to obtain normal values in newborns, we analysed the M-mode echocardiograms of 60 newborn infants without heart disease by computer, as first described by Gibson and Brown.[1]

During fetal life, both cardiac ventricles function in parallel, the right ventricle pumping about two thirds and the left ventricle about one third of the combined cardiac output. After birth, both ventricles function in series; while the right ventricular output remains unchanged, the left ventricular output increases by about one third of its prenatal volume.[2-4] In order to investigate the adaptation of the left ventricle to this higher volume load immediately after birth, we examined in addition left ventricular cavity dimensions and contractility variables in 15 healthy newborns sequentially during the first hour of postnatal life.

Methods

M-mode echocardiograms were obtained in 60 newborns without heart disease according to a method described by Solinger *et al.*[5] Twenty nine of the newborns were female and 31 were male, their ages ranging from 3 to 7 days. The mean body weight was 3206 g, the mean body length 49·4 cm. An unfocused 5 MHz transducer with an active crystal diameter of 6 mm was used. The echocardiograms were obtained in the usual manner while the newborns were lying supine or in slight left decubitus position. Recordings were made at a paper speed of 100 mm per second.

Echoes of the right and left ventricular cavity and of the interventricular septum were obtained at the level of the mitral valve. The echoes of three to four consecutive cardiac cycles were digitised using an x-y tablet with cursor and processed by computer* using a program especially developed for this purpose. For time reference the beginning of the corresponding QRS complexes of the electrocardiogram was digitised. The computer provided plots of continuous right and left ventricular cavity dimensions as well as septal and left ventricular wall thickness.

The following variables were measured or calculated, respectively: the end-diastolic diameter (D_o) of the right and left ventricle at the beginning of the QRS complex, the shortest end-systolic diameter (D_{min}) of the right and left ventricle, the percentage

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*Cardio 80 Fa. Kontron.

change of ventricular diameter in systole (SF) calculated according to the formula

$$SF = \frac{D_o - D_{min}}{D_o} \times 100\,(\%),$$

and the normalised velocity of change of ventricular dimension VCF calculated according to the formula $VCF = \frac{1}{D} \times \frac{dD}{dt}$ per second (Fig. 1) (this latter variable is independent of ventricular size and thus allows comparison between ventricles of different sizes). The results are expressed as the maximal shortening velocity of the left and right ventricular diameter during systole (VCF_{min}) and the maximal velocity of lengthening of the left and right ventricular diameter during diastole (VCF_{max}). The thickness of the interventricular septum ($D_{o\ ivs}$) and the left ventricular posterior wall ($D_{o\ pw}$) at the beginning of the QRS complex, the maximal thickness of the interventricular septum ($D_{max\ ivs}$) and of the left ventricular posterior wall ($D_{max\ pw}$), and the percentage of systolic thickening (ΔD (%)) of the interventricular septum and posterior left ventricular wall were also measured or calculated, respectively. The mean values of three to four consecutive cardiac cycles were taken as representative. The heart rate was calculated from the simultaneously recorded electrocardiogram.

Measurements and calculations were done only if the echoes were clearly identifiable and could be analysed continuously throughout the cardiac cycles. The left ventricular diameter and derived variables were obtained in all 60 newborns. The left ventricular posterior wall could be analysed in 56, the interventricular septum in 43, and the right ventricle in 23 newborns.

In addition, 15 newborns were studied several times during the first hour of life after normal delivery. Left ventricular echocardiograms were obtained in consecutive intervals of 10 minutes, beginning at 10 minutes and ending 60 minutes after birth. The echocardiograms were recorded and analysed as described above.

For statistical analysis a one factor randomised block design for the variables D_o, D_{min}, SF, VCF_{min}, and VCF_{max} was done.[6] The global significance level was assumed to be 5%. For testing the time differences a simultaneous test procedure as described by Gabriel was done. For the variable SF a trend analysis was performed.[7]

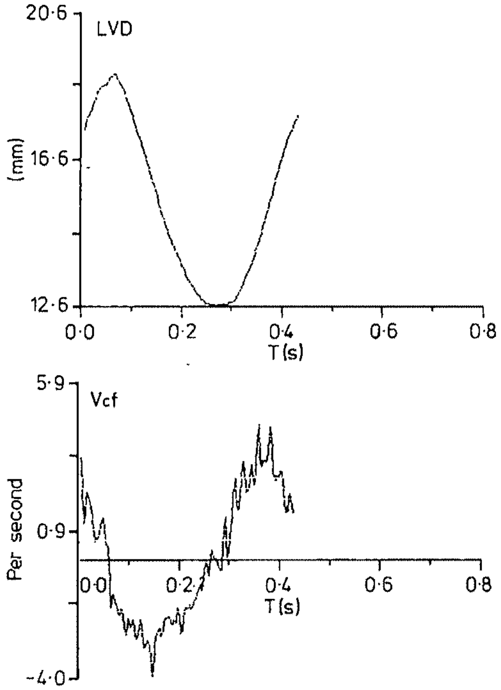

Fig. 1 *Upper panel: left ventricular diameter (LVD) during one cardiac cycle. Lower panel: unsmoothed curve of normalised velocity of change of left ventricular diameter (VCF) during the same cardiac cycle as shown in the upper panel.*

Results

The results for both ventricles are summarised in Table 1, and those for the interventricular septum and left ventricular posterior wall in Table 2.

The left ventricle has an end-diastolic diameter of 15·7±2·1 mm (mean±SD) and a systolic diameter of 10·3±2·1 mm. The percentage change of left ventricular diameter in systole is 34·3±8·2%. The maximal velocity of shortening (VCF_{min}) and lengthening

Table 1 *M-mode echocardiographic variables of right and left ventricle in 60 newborns 3 to 7 days of age*

	D_o±SD (mm)	*D_{min}±SD (mm)*	*SF±SD (%)*	*VCF_{min}/s (±SD)*	*VCF_{max}/s (±SD)*
Right ventricle n=23	10·0±1·8	7·7±1·6	22·4±9·6	−4·07±2·25	4·3±2·09
Left ventricle n=60	15·7±2·1	10·3±2·1	34·4±8·2	−4·64±1·49	6·28±3·13

Table 2 *M-mode echocardiographic variables of interventricular septum and left ventricular posterior wall in 60 newborns 3 to 7 days of age*

	D_o±SD (mm)	D_{max}±SD (mm)	△D±SD (%)
Interventricular septum n=43	4·5±1·3	6·1±1·4	39·8±17·2
Left ventricular posterior wall n=56	3·1±0·7	5·2±0·9	73·8±44·6

($V_{CF_{max}}$) of the left ventricular diameter is 4·64±1·49 and 6·28±3·13 per second, respectively. The end-diastolic diameter of the right ventricle measures 10·0±1·8 mm, the end-systolic diameter 7·7±1·6 mm. The percentage change of right ventricular diameter is 22·4±9·6 (%). $V_{CF_{min}}$ and $V_{CF_{max}}$ of the right ventricle are 4·07±2·25 and 4·3±2·09 per second, respectively. The interventricular septum has a mean end-diastolic thickness of 4·5±1·3 mm and a maximal systolic thickness of 6·1±1·35 mm. The percentage systolic increase in thickness of the interventricular septum amounts to 39·8±17·2%.

End-diastolic and maximal systolic thickness of the left ventricular posterior wall are 3·1±0·7 mm and 5·2±0·85 mm, respectively. The percentage systolic increase in posterior wall thickness is 73·8±44·6%.

Large variance prevented us from calculating the velocity of change in thickness of the interventricular septum and left ventricular posterior wall.

The results of the study of 15 normal newborns during the first hour of life are shown in Table 3. During the first hour of life the left ventricular end-diastolic diameter (D_o) increased significantly from 15·5±3·2 mm 10 minutes after birth to 17·1±3·1 mm 60 minutes after birth ($p<0·01$); in contrast, the end-systolic diameter remained unchanged at 11·0±2·7 and 11·1±2·4 mm, respectively. Accordingly, the percentage change of left ventricular diameter in systole (SF) increased from 29·2±7·4% 10 minutes after birth to 35·6±5·2% 60 minutes after birth ($p<0·005$) in a linear fashion. $V_{CF_{min}}$ showed a slight but not significant increase from 4·29±1·2 per second 10 minutes after birth to 4·93±1·0 per second 60 minutes after birth ($0·1>p>0·05$) (Fig. 2). $V_{CF_{max}}$ increased but not significantly from 5·6±2·1 at 10 minutes to 6·4±2·0 per second 60 minutes after birth. The heart rate remained stable at 161±13 and 158±15 beats per minute, respectively.

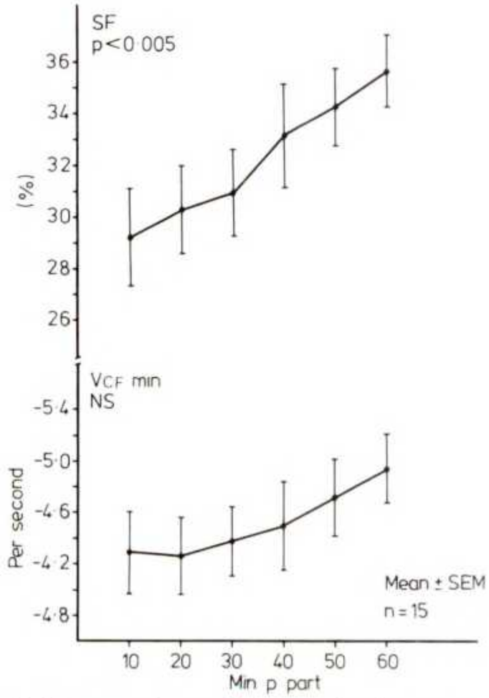

Fig. 2 *Percentage change of left ventricular diameter in systole (SF) (upper panel) and maximal shortening velocity of the left ventricular diameter during systole ($V_{CF_{min}}$) (lower panel) during the first hour of life in 15 normal newborns. The difference between the values at 10 and 60 minutes of life for SF is statistically significant ($p<0·005$) while for $V_{CF_{min}}$ it is not significant ($0·1>p>0·05$).*

Discussion

There are few echocardiographic studies systematically examining ventricular function and dynamics in normal newborn infants. Sahn *et al.*[8] found a significant increase in mean VCF, a variable comparable to SF, during the first hour of life in seven newborn

Table 3 *M-mode echocardiographic variables of left ventricle in 15 newborns 10, 20, 30, 40, 50, and 60 minutes of age*

Minutes after birth	D_o (mm)	D min (mm)	SF (%)	$V_{CF_{min}}$/s	$V_{CF_{max}}$/s	HR/min
10	15·5±3·2	11·0±2·7	29·2±7·4	4·3±1·2	5·6±2·1	161±13
20	16·6±2·4	11·7±2·1	30·3±6·6	4·3±1·2	5·6±2·3	155±11
30	16·9±2·6	11·7±2·5	30·9±6·6	4·4±1·0	5·6±1·9	160±13
40	17·3±2·5	11·8±2·6	33·1±7·7	4·4±1·3	5·5±2·4	155±10
50	16·7±3·0	11·1±2·5	34·2±5·8	4·7±1·1	6·1±3·1	155±14
60	17·1±3·1	11·1±2·4	35·6±5·2	4·9±1·0	6·4±2·0	158±15

infants after caesarian section. St John Sutton *et al.*[9] investigated cardiac function in the normal newborn using computer analysis; the results of the variables studied both in their work and in this study are comparable. Lange *et al.*,[10] comparing left and right ventricular diameters before and after birth, found a decrease in the right ventricular diameter after birth while the left ventricular diameter remained unchanged.

Comparing the data of normal newborns with those from three to seven days after birth, we found that the left ventricular end-diastolic diameter increased from 10 minutes to 60 minutes after birth but, at the age of 3 to 7 days, it equalled the former value. The percentage change of left ventricular diameter in systole (SF) also increased from 10 minutes to 60 minutes after birth but was found unchanged at 3 to 7 days after birth.

The change during the first hour of life may be the result of the postnatal increase in left ventricular volume work. During fetal life right and left ventricles function in parallel. In the fetal lamb the left ventricle pumps 150 ml/kg per min and the right ventricle 200 ml/kg per min, respectively. After birth, both ventricles pump in series 200 ml/kg per min. This implies an increase in left ventricular output of 33%.[4] At the same time, the left ventricular systolic pressure increases from 60 mmHg before to 75 mmHg after birth. This increase in systolic pressure is most probably the result of closure of the low resistance placental circulation.[3] Gessner *et al.*[11] studied the left and right ventricular output in the first two hours of life using the indicator dilution technique. They found a higher left than right ventricular output caused by ductal left to right shunt at this age. Emmanouilides *et al.*[12] also found a left to right ductal shunt with higher left than right ventricular outputs in the first hours of life. Thirteen to 15 hours postnatally they found the ductus arteriosus functionally closed in all newborns.[12]

The fact that the left ventricular end-diastolic diameter (D_o) increases in the first hour of life, but that at the age of 3 to 7 days it is equal to the value at 10 minutes of age may reflect adaptation of the left ventricle to increased work using the Frank-Starling mechanism.

We conclude that left ventricular contractility in normal newborns increases during the first hour of life and, at 1 hour of life, it is identical to that of older newborns, infants, and children.[13] [14]

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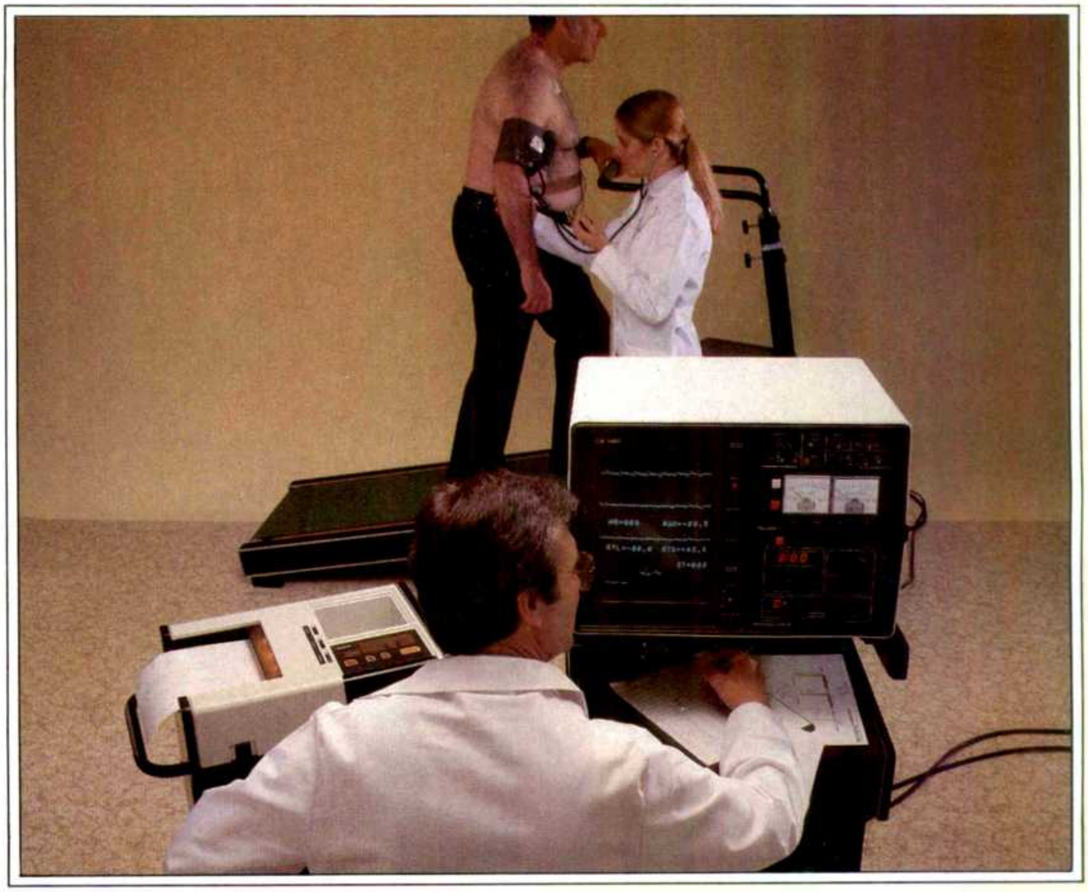

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Clinical, echocardiographic, and operative findings in active infective endocarditis

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SUMMARY Clinical and echocardiographic findings were compared with those found at operation in 18 consecutive patients with active endocarditis undergoing valve replacement for continuing left ventricular failure. A close correlation was shown between vegetations detected by echocardiography and those found at operation. In 10 of 11 patients with clinically suspected severe aortic regurgitation and vegetations only on the aortic valve and in two of three patients with severe mitral regurgitation echocardiography provided confirmation of the clinical diagnosis. In the three patients with clinically suspected aortic and mitral regurgitation, however, cardiac catheterisation was necessary to confirm the severity of the valvular regurgitation. In a further three patients cardiac catheterisation was carried out as the severity of the single valve lesion was difficult to assess or there were associated problems, that is chest pain with myocardial infarction and a sinus of Valsalva aneurysm. Four patients had either an abscess, annular infection, a sinus, or a ventricular septal defect at the time of operation, which were not detected by echocardiography. Nevertheless, because of their size it would be doubtful if these would have been identified by cardiac catheterisation. Echocardiography allowed repeated assessment of the patient so that the optimal time for operation could be determined without the risks of left heart catheterisation. Fourteen of the 18 patients (78%) survived to leave hospital. The follow-up extended to 44 months. During this time reinfection, prosthetic dehiscence, or paravalvular leaks did not occur. Thus, in the majority of patients with left sided active infective endocarditis and continuing left ventricular failure resulting from severe valvular disease the clinical findings together with echocardiography provide a satisfactory preoperative assessment.

In patients who develop haemodynamic complications of endocarditis, early surgical intervention is increasingly used.[1-3] Aortic or mitral valve endocarditis complicated by moderate to severe heart failure has a poor prognosis when treated by medical therapy alone.[4 5] It has been suggested that in these patients with moderate to severe heart failure there is a 50 to 89% mortality without operation.[4] Valve replacement in the presence of active infection can now be carried out with an acceptable mortality, and in addition the risk of recurrent infection or valve dysfunction is low.[6] Confirmation of the haemodynamic status and valvular lesions by cardiac catheterisation is theoretically desirable but should carry an increased risk of systemic embolisation considering the natural history of the disease. Echocardiography is a useful non-invasive means of identifying valvular vegetations but both M-mode and two dimensional echocardiography have a limited sensitivity in the detection of vegetations. It has been suggested that the smallest vegetations detected by M-mode echocardiography are 2 mm in diameter.[7 8] The larger vegetations which often result in valvular destruction and regurgitation are recognised by echocardiography and it is in these patients that operation is frequently necessary.[5 8 9] Though it is desirable to eradicate the infection before correction of the valve lesion, when uncontrolled heart failure develops during the course of antibiotic treatment, surgical correction of the valvular defect is urgent. In this study we compared the clinical and echocardiographic findings with those found at operation in patients with active endocarditis undergoing valve replacement because of continuing left ventricular failure despite digitalis and diuretics.

Patients and methods

Eighteen consecutive patients with active infective endocarditis were studied from 1978 to 1981. There were 13 male and five female cases (13 to 65, mean 45

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years). Twelve had class 4 clinical degree of heart failure (New York Heart Association classification) and six were in class 3. On clinical assessment, 11 patients had aortic regurgitation, one had aortic stenosis, three had mitral regurgitation, and three had aortic and mitral regurgitation. All patients therefore had left sided endocarditis and in all this was the first episode of endocarditis. Active infective endocarditis was diagnosed by varying manifestations, for example fever, changing cardiac murmurs, splenomegaly, haematuria, peripheral embolisation, and petechiae, and by laboratory evidence, including a high erythrocyte sedimentation rate, anaemia, positive blood cultures, and histopathology. In 12 patients the causative organism was isolated preoperatively and in six patients no organisms were cultured (Table 1).

Seven of the 18 patients were known to have had heart murmurs before the development of endocarditis. One patient was a chronic alcoholic and in one patient cardiac surgery was possibly a predisposing factor. No patient suffered from neoplasia or drug addiction. At the time of presentation six patients had had systemic emboli, involving either the cerebral or peripheral arteries, four had heart block (three with first degree atrioventricular block and one with complete heart block not resulting from digoxin), and two patients had had several episodes of severe central chest pain, one of whom had had an acute lateral infarction.

M-mode echocardiography was carried out in all 18 patients using a Smith Kline instruments Ekoline 20 A system with standard left parasternal views. Immediately after the M-mode echocardiogram, two dimensional echocardiography was performed in 16 patients with a Varian phased array ultrasonograph model V—3000. Long and short axis left parasternal views and four chamber apical or subcostal views were obtained in all 16 patients. An attempt was made to visualise all four valves in each patient. Images were recorded on a Sony video tape recorder for subsequent play back and single frame analysis. Satisfactory echocardiograms were obtained in all 18 patients. Valvular vegetations were detected by M-mode echocardiography as shaggy irregular echoes attached to a valve which had unrestricted leaflet excursion (Fig. 1). On two dimensional echocardiography rapidly vibrating echo dense masses attached to valve leaflets were interpreted as vegetations (Fig. 2, 3, 4, and 5). Chamber size and timing of events could be assessed by M-mode echocardiography whereas spatial relation and actual size and morphology of structures were determined by two dimensional echocardiography. Rupture or perforation of an aortic cusp or prolapsing vegetations were suggested by left ventricular outflow tract echoes recorded in diastole and rapidly vibrating diastolic aortic cusp echoes on M-mode echocardiography (Fig. 6). The early closure of a mitral valve was indicated when coaptation of the anterior and posterior leaflets of

Table 1 *Clinical, echocardiographic, and surgical findings in 18 patients with active infective endocarditis*

Case No.	*Age/Sex (y)*	*Clinical findings*	*Organism*	*Echo findings*	*Operative findings*	*Operative procedure*	*Survived or died*
1	60/F	AR	*E.coli*	AVV,LVOT,EC	AVV,LVOT(PVC)	AVR	S
2	45/M	AR	*Strep. viridans*	AVV,LVOT,EC	AVV,LVOT(PVC)	AVR	S
3	27/M	AR	Staph coag$^+$	AVV,LVOT,EC	AVV,LVOT(PVC), sinus to mitral valve	AVR, closure of sinus	D
4	39/M	AR	Staph coag$^+$	AVV,LVOT	AVV,LVOT(PVC), abscess in aortic wall	AVR, abscess debrided	S
5	26/F	MR	Culture neg	MVV,FML	MVV,CR	MVR	S
6	60/M	AR	*Strep. D*	AVV,LVOT	AVV,LVOT(PVC)	AVR	S
7	54/M	AR,MR	*Strep.viridans*	AVV,LVOT	AVV,LVOT(PVC), healed MVV,CR	AVR,MV repair	S
8	37/M	AR	Staph coag$^+$	No vegetations	AVV,MVV	AVR	S
9	63/M	AR,MR	Culture neg	AVV,LVOT	AVV	AVR	S
10	59/F	AR	Culture neg	AVV,LVOT,EC	AVV,LVOT(PVC)	AVR	S
11	44/F	AR,MR	Strep.C	AVV,MVV,FML	AVV,MVV,CR	AVR,MVR	S
12	55/M	MR	*Strep.viridans*	MVV,FML	MVV,CR	MVR	S
13	54/F	MR	Staph coag$^-$	No vegetations	MVV	MVR	D
14	27/M	AR	Staph coag$^+$	AVV,LVOT	AVV,LVOT(PVC)	AVR	S
15	13/M	AS	Culture neg	AVV, sinus of Valsalva aneurysm	AVV,AMI, sinus of Valsalva aneurysm	AVR,SVG to Cx	D
16	49/M	AR	Culture neg	AVV,LVOT,EC	AVV,LVOT(PVC),AV ring infection	AVR	D
17	34/M	AR	*Strep.viridans*	AVV,LVOT,EC	AVV,LVOT(PVC),VSD	AVR, closure of VSD	S
18	65/M	AR	Culture neg (psittacosis titre 1:5120)	AVV,LVOT	AVV,LVOT(PVC)	AVR	S

AR, aortic regurgitation; MR, mitral regurgitation; AS, aortic stenosis; AVV, aortic valvular vegetations; LVOT, left ventricular outflow tract echoes; EC, early closure of the mitral valve; MVV, mitral valve vegetations; FML, flail mitral leaflet; LVOT(PVC), left ventricular outflow tract (prolapsing vegetation and/or cusp); CR, chordal rupture; AMI, acute myocardial infarction; VSD, ventricular septal defect; AVR, aortic valve replacement; MVR, mitral valve replacement; SVG, saphenous vein graft; Cx, circumflex.

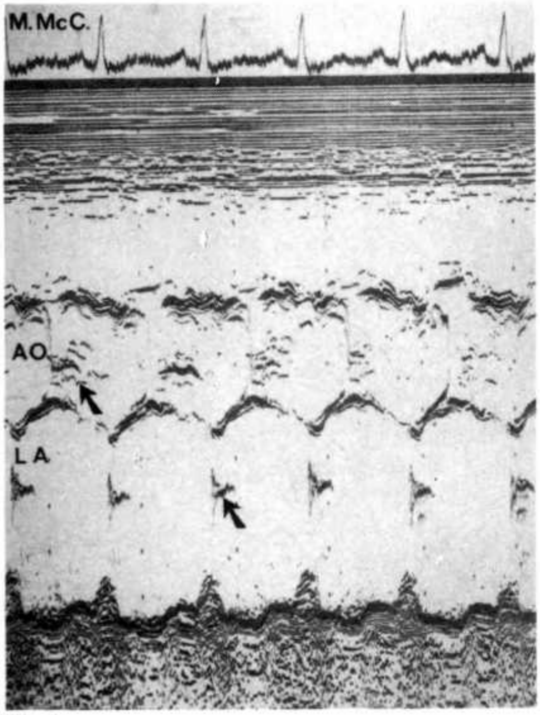

Fig. 1

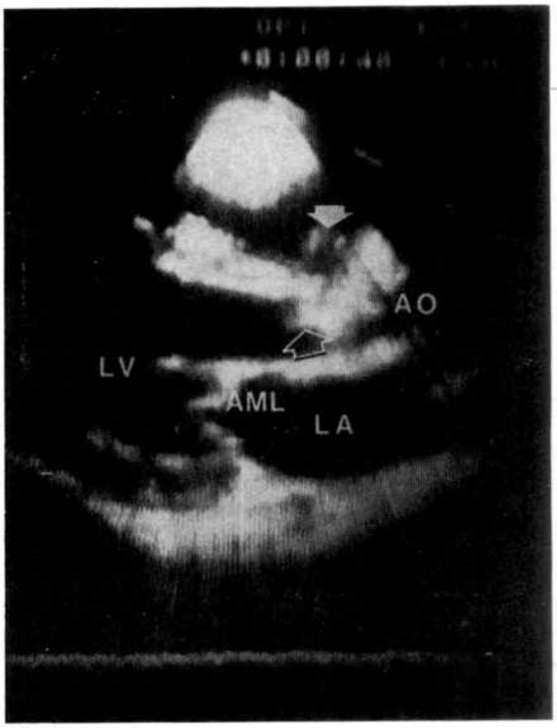

Fig. 3

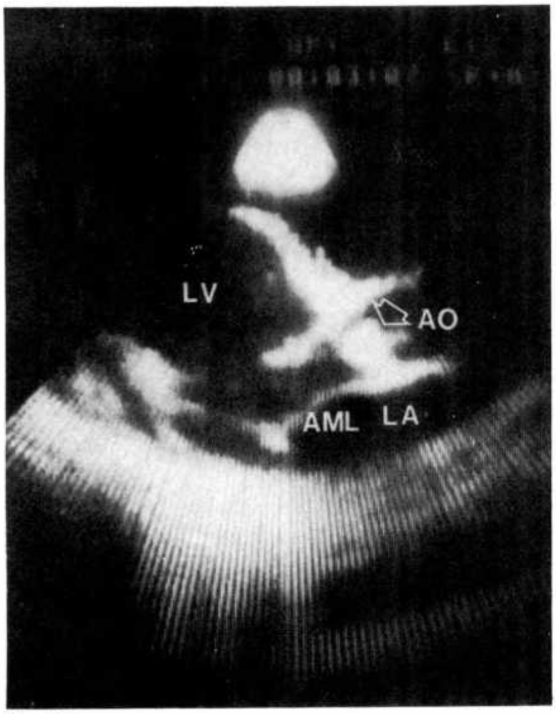

Fig. 2

Fig. 1 *M-mode echocardiogram of case 11 showing vegetations (arrow) on the aortic valve in diastole. The echoes (arrow) in the left atrium represent vegetations on the mitral valve prolapsing into the left atrium during systole. AO, aorta; LA, left atrium.*

Fig. 2 *Two dimensional echocardiogram of case 2 in the left parasternal long axis view showing a globular vegetation on the non-coronary cusp of the aortic valve (open arrow). The right coronary cusp with a vegetation attached is seen prolapsing into the left ventricular outflow tract (tongue-like structure). LV, left ventricle; AO, aorta; AML, anterior mitral leaflet; LA, left atrium.*

Fig. 3 *Two dimensional echocardiogram of case 15 in the left parasternal long axis view with a globular vegetation on the aortic valve (open arrow). Anterior to the aortic valve is an echo-free cavity (closed arrow) which was found at surgery to be a sinus of Valsalva aneurysm. LV, left ventricle; AO, aorta; AML, anterior mitral leaflet; LA, left atrium.*

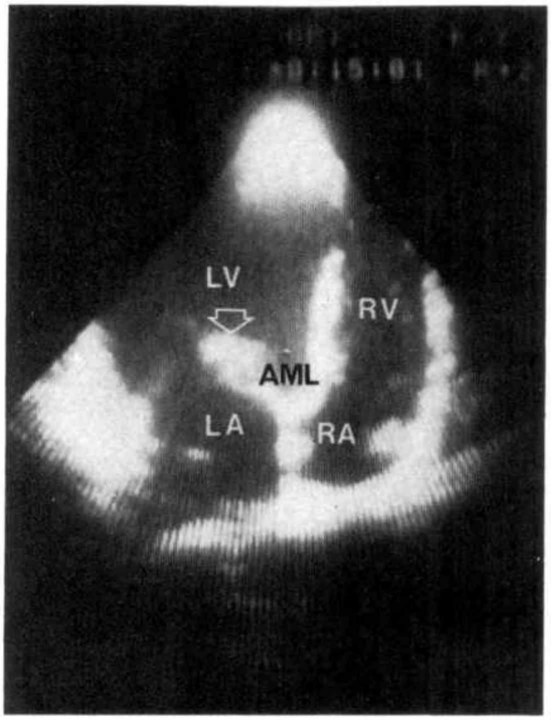

Fig. 4 *Two dimensional echocardiogram of case 12 in the apical four chamber view with vegetations attached to the anterior mitral leaflet (open arrow). LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; AML, anterior mitral leaflet.*

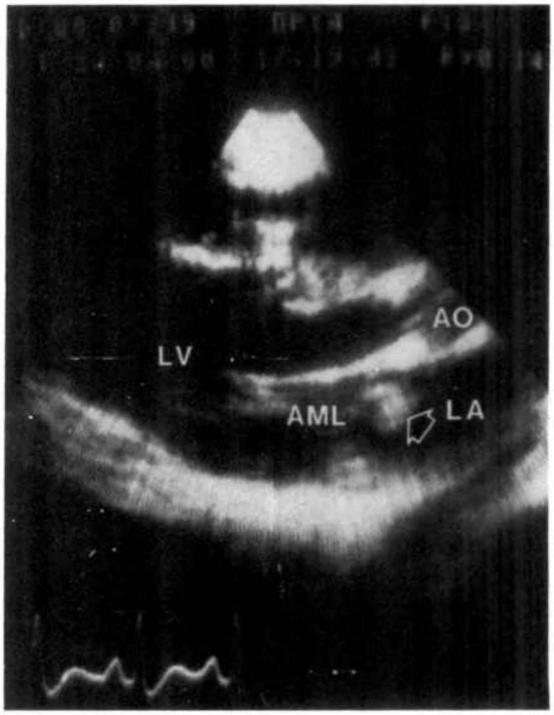

Fig. 5 *Two dimensional echocardiogram of case 11 in the left parasternal long axis view with a globular vegetation on the mitral valve prolapsing into the left atrium (open arrow). The vegetation on the aortic valve is not well visualised in this view. LV, left ventricle; AO, aorta; AML, anterior mitral leaflet; LA, left atrium.*

the mitral valve occurred before the onset of the QRS segment in the absence of prolongation of the PR interval (Fig. 6). This indicated significant aortic regurgitation with a rise in the left ventricular end-diastolic pressure. Mitral valve chordal rupture was present when there was coarse irregular fluttering of either mitral valve leaflet with paradoxical motion of the posterior leaflet and abnormal left atrial echoes (Fig. 7). The average time from the last echo to operation was 15 days (12 patients within seven days).

All patients before operation were receiving appropriate antibiotics. The average time from the onset of symptoms to the start of antibiotic treatment was seven weeks and the mean duration of antibiotic treatment at the time of operation was 36 days. One patient had received antibiotics for only 48 hours at the time of operation; these were given in an attempt to sterilise the circulation before essential valve replacement. At the time of operation blood cultures in all patients except one were negative, but two patients had persistent pyrexia.

The presence of vegetations alone on echocardiography was not an indication per se for operation.[10 11] Surgical intervention was indicated when patients with severe aortic stenosis or with new or worsening regurgitant murmurs developed left ventricular failure as diagnosed clinically and by chest x-ray film which did not respond satisfactorily to diuretics and inotropic therapy. Only six patients underwent cardiac catheterisation before operation. In cases 6 and 13 (mitral Starr-Edwards prosthesis) it was carried out as it was difficult clinically to determine the severity of the lesion. In cases 7, 9, and 11 cardiac catheterisation was carried out because of clinically suspected double valve lesions. In all three patients mitral and aortic regurgitation were haemodynamically significant. In case 15 it was carried out because of severe aortic stenosis, continuing chest pain in the presence of a lateral myocardial infarction, and an echocardiogram suggesting a sinus of Valsalva aneurysm. At the time of catheterisation this patient was found to have severe aortic stenosis with a sinus of Valsalva aneurysm which stretched the mouth of the left coronary artery and constricted the lumen.

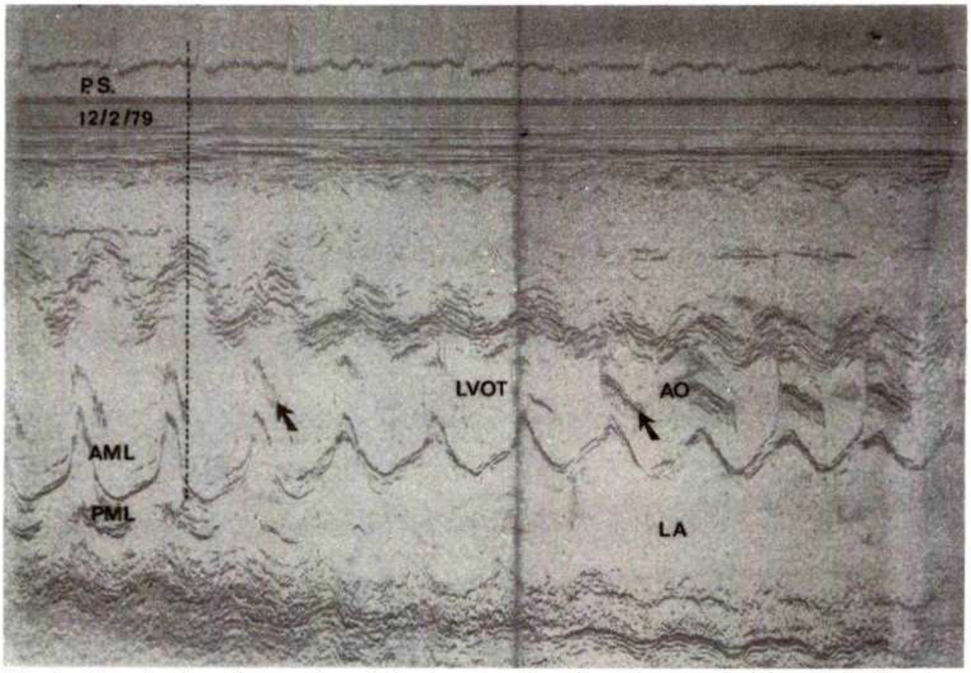

Fig. 6 *M-mode echocardiogram of case 2 showing a scan from the aortic root to the left ventricle. There is a vegetation attached to the aortic valve which prolapses into the left ventricular outflow tract (arrows). The mitral valve closure is premature which indicates a raised left ventricular end-diastolic pressure secondary to aortic regurgitation. AML, anterior mitral leaflet; PML, posterior mitral leaflet; LVOT, left ventricular outflow tract; AO, aorta; LA, left atrium.*

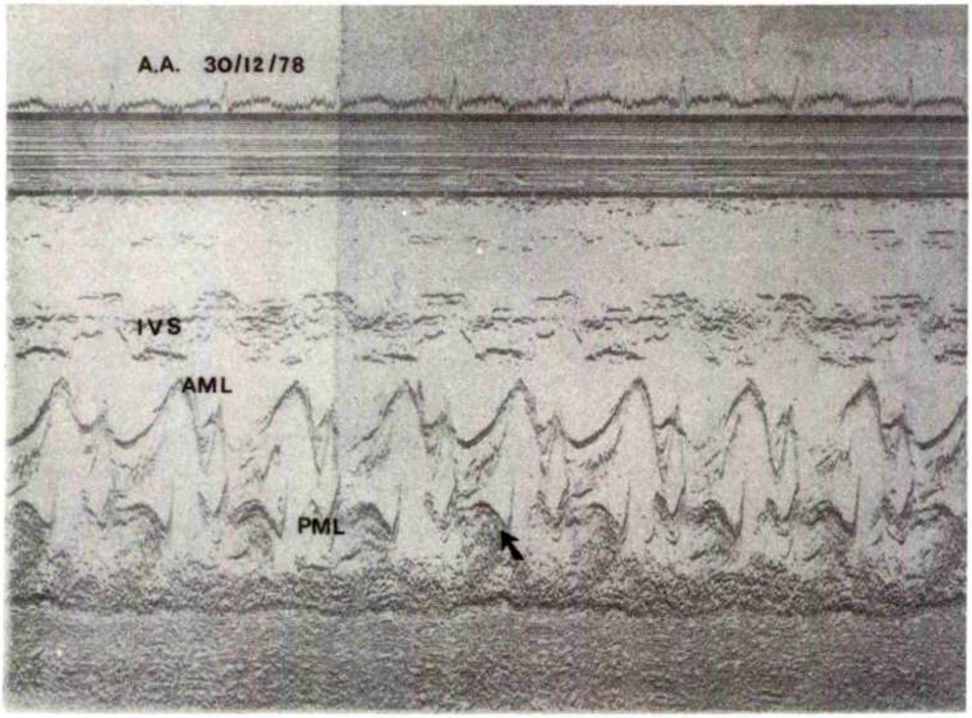

Fig. 7 *M-mode echocardiogram of case 12 with a vegetation attached to the posterior mitral leaflet (arrow) which is flail. AML, anterior mitral leaflet; PML, posterior mitral leaflet; IVS, interventricular septum.*

Results

Echocardiography detected valvular vegetations before operation solely on the aortic valve in 13 patients, on the mitral valve only in two patients, and one patient had both aortic and mitral valve vegetations (Table 1). Two patients (cases 8 and 13) had no vegetations on echocardiography. Case 13 had a mitral Starr-Edward's prosthesis. Intially case 15 with aortic stenosis had no vegetations on the aortic valve as seen by echo (Fig. 8). He then developed severe chest pain and left ventricular failure. A second study nine days later showed aortic valvular vegetations and a sinus of Valsalva aneurysm (Fig. 3 and 8). Though cases 13 and 16 did not have two dimensional studies performed, no patient had a negative M-mode echocardiogram with valvular vegetations seen on two dimensional study. Twelve of the 13 patients with aortic valve vegetations alone had evidence of valve destruction as indicated by left ventricular outflow tract echoes and in six of these there was early mitral valve closure. Cases 5, 11, and 12 with vegetations by echocardiography on the mitral valve had flail mitral leaflets, but case 11 with double mitral and aortic lesions had vigorous aortic root motion suggesting severe mitral regurgitation.

Operation confirmed aortic vegetations in all 13 patients with vegetations only on the aortic valve detected by echocardiography. All underwent aortic valve replacement and one patient (case 7) also had a mitral valve repair. Two patients with mitral valve vegetations alone by echocardiography had these confirmed at operation and both underwent mitral valve replacement and the one patient with aortic and mitral vegetations confirmed at operation had aortic and mitral valve replacements. Two patients without vegetations recorded by echocardiography had these at operation. In one patient (case 8) the aortic valve was grossly disrupted at the time of operation with a vegetation found on the undersurface and there was also a small vegetation on an otherwise competent mitral valve. Case 13 had vegetations on a mitral Starr-Edwards prosthesis. In addition, case 7 had a vegetation on the mitral valve not seen by echocardiogram before operation.

Four patients had unexpected findings at operation and none had undergone cardiac catheterisation. One (case 3) had a sinus extending from the base of an aortic cusp to the mitral valve ring, one (case 4) had an abscess underneath the non-coronary cusp of the aortic valve, another (case 16) had infection within the aortic

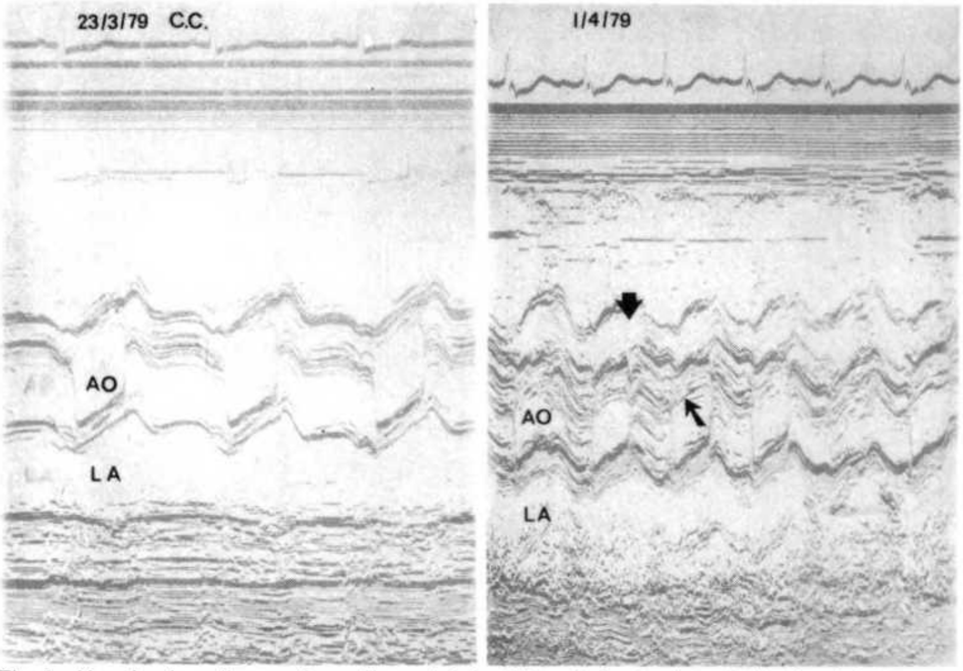

Fig. 8 *M-mode echocardiogram of case 15 on admission (left) and nine days later (right). On admission there is eccentric opening and closure of the aortic valve. Nine days later there are aortic valvular vegetations (small arrow) and an echo-free space has occurred in front of the aortic root (large arrow). AO, aorta; LA, left atrium.*

valve ring, and a further patient (case 17) had an aneurysm of the membranous septum with a small ventricular septal defect.

Table 2 relates the valvular lesions to the echocardiographic findings and to those found at operation. While a close correlation is shown between the echocardiographic and surgical findings it confirms that at operation four valves had vegetations not seen by echocardiography. In addition, in four patients presenting with aortic regurgitation alone a sinus, annular erosion, abscess, and a ventricular septal defect not detected by echocardiography were found at operation.

Of the 15 aortic valves replaced, 11 were bicuspid and four were tricuspid. Because of severe damage to the four tricuspid valves it was impossible to ascertain the most likely cause of the underlying disease. Of the four mitral valves replaced, one was rheumatic, one was floppy, one was a Starr-Edwards prosthesis, and one had been normal before endocarditis. Of the three mitral valves found to be abnormal at the time of operation, and which were not replaced, one had chordal rupture associated with a healed vegetation and valvuloplasty was carried out, one patient had a dilated mitral valve ring, and a further patient had a vegetation attached to the mitral valve. Histology of all valves removed confirmed active infection. Of the 19 valves removed, 12 were replaced by a Carpentier-Edwards prosthesis, four by a Björk-Shiley, and three by a St. Jude's.

Apart from case 15 who died during the operation from left ventricular dysfunction and acute myocardial infarction, all patients were haemodynamically stable immediately after operation. There were three deaths later during their hospital stay. Case 3 died on the ninth day postoperatively from multiple abscesses, case 13 died on the first day from asystole, and case 16 died on the fifteenth day from hepatic and renal failure. This patient had been a chronic alcoholic. During the period in hospital there was no evidence of continuing infection, and prosthetic dehiscence, paravalvular leaks, and heart block did not occur in the remaining patients. The average course of antibiotics postoperatively was three to six weeks. Follow-up ranged from three to 44 months (mean 22 months). During this time, there was no evidence of reinfection of any of the replaced valves, nor was there any regurgitation.

Discussion

Although antibiotics have substantially changed the course of the disease in many patients, infective endocarditis still carries a significant mortality mainly because of valvular destruction which results in myocardial failure.[12] At present, the leading cause of death from infective endocarditis is congestive heart failure developing from acute aortic regurgitation. Since valve replacement was first described in this condition in 1965[13] it is increasingly performed even in the presence of active infection. Often these patients have deteriorated acutely and clinical assessment of the exact valvular lesion can be difficult because of low cardiac output and hypotension.

Although echocardiography is a valuable non-invasive means for the diagnosis of valvular vegetations in patients with endocarditis it has been reported that vegetations are detected in 34% to 78% of cases, depending on the size of the vegetations.[6] [14] Large valvular vegetations detected by echocardiography are usually associated with a high incidence of heart failure or emboli, which are the most frequent indications for operation. Though in patients with large vegetations it has been considered that operation is inevitable as these patients have a high morbidity and mortality, successful medical treatment has been reported in some.[15] Vegetations causing valvular destruction are, however, of large size, are diagnosed easily by echocardiography, and in many are associated with haemodynamic complications unresponsive to medical treatment. In this study a close correlation has been shown between valvular vegetations detected by

Table 2 *Echocardiographic and surgical findings related to the valvular lesions in 18 patients with active infective endocarditis*

Clinical		*Echocardiography*						*Surgical*						
	No. of patients	*AVV*	*LVOT*	*EC*	*MVV*	*FML*	*Sinus of Valsalva aneurysm*	*AVV*	*Vegetation and/or cusp prolapsing into LVOT*	*MVV*	*Chordal rupture of mitral valve*	*Sinus or abscess in aortic wall*	*VSD*	*Sinus of Valsalva aneurysm*
AR	11	10	10	6	0	0	0	11	10	1	0	3	1	0
AS	1	1	0	0	0	0	1	1	0	0	0	0	0	1
MR	3	0	0	0	2	2	0	0	0	3	2	0	0	0
AR,MR	3	3	2	0	1	1	0	3	1	2	2	0	0	0

AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; AVV, aortic valvular vegetations; LVOT, left ventricular outflow tract echoes; EC, early closure of the mitral valve; MVV, mitral valve vegetations; FML, flail mitral leaflet; VSD, ventricular septal defect.

echocardiography and those found at operation. As M-mode and two dimensional echocardiography complement each other, it is not surprising that both M-mode and two dimensional echocardiography were equally sensitive in the detection of vegetations in this particular subset of patients. Two patients without vegetations detected by echocardiography were subsequently found to have vegetations at operation. Case 13 was studied by M-mode echocardiography only and the vegetations on the mitral Starr-Edwards valve were not identified. The prosthetic valve is usually so echo producing in itself that it is difficult to identify any additional echoes from possible vegetations. Others have found two dimensional echocardiography more accurate in such cases.[16] Echocardiography is also useful in assessing left ventricular function and provides valuable information in those with hypotension and low cardiac output. Premature closure of the mitral valve in acute aortic regurgitation is usually an indication for early surgical replacement of the valve.[2 17] Early closure of the mitral valve implies a severely volume overloaded left ventricle, and it is thought that when severe aortic regurgitation is of relatively short onset, this results in mitral preclosure.[18 19] Unfortunately, some patients with acute severe aortic regurgitation do not have this echocardiographic finding.

Echocardiography provided support for the correct anatomical diagnosis in 10 of 11 patients with clinically suspected severe aortic regurgitation and vegetations only on the aortic valve and in two of three patients with severe mitral regurgitation alone. In the three patients with clinically suspected aortic and mitral regurgitation, however, only one patient had double valvular involvement by echocardiography and yet all three had significant mitral and aortic regurgitation by angiography. Here M-mode and two dimensional echocardiography detected the sinus of Valsalva aneurysm. Nevertheless, abscesses, annular erosions, sinuses, and small ventricular septal defects are difficult to detect by echocardiography. Of the four in this study, none was detected before operation. It would be doubtful if these would have been picked up by cardiac catheterisation. It has been reported that two dimensional echocardiography is more sensitive than M-mode echocardiography in detecting complications of endocarditis.[20 21] It has been stated that aortic root infection should be suspected in the presence of atrioventricular block.[22] Of the four patients in this study with atrioventricular block, one had infection of the aortic valve ring, one had a ventricular septal defect, but in the remaining two there was no evidence of aortic root infection. Of the two patients with chest pain, one had a sinus of Valsalva aneurysm stretching the mouth of the left coronary artery and the other had a ventricular septal defect with intermittent atrioventricular block.

Wilson *et al.*[23] have found that replacement of cardiac valves may be carried out successfully in patients with active infective endocarditis even when blood cultures are positive in the immediate preoperative period. The haemodynamic status, however, is the most important factor in determining the timing of valve replacement. While the activity of the infection or the duration of antimicrobial treatment before operation may be of little or no importance in the decision to insert a prosthesis, ideally attempts should be made to eradicate the infection before operation. Antibiotics should be administered until at least the circulation is sterilised but heart failure should not be irreversible. In our patients we feel that the timing was critical in determining long-term survival and echocardiography allowed repeated investigation to determine the optimal time haemodynamically without the risks of left heart catheterisation.[22]

Although Welton *et al.*[24] have reported catheterisation in 35 patients during the active phase of endocarditis without embolic or haemodynamic deterioration, cardiac catheterisation must carry an increased risk during this phase as valvular vegetations are friable and systemic embolisation is part of the natural history of the disease. Frequently severe haemodynamic decompensation may increase the risk of complications during cardiac catheterisation. In these 18 patients one third had had systemic emboli at the time of presentation and others have reported a higher incidence.[8] Our study indicates that cardiac catheterisation is unnecessary in many of these patients during the acute phase. It should be considered when the echocardiographic studies are not technically adequate, when double valvular lesions, coronary artery lesions and fistulae are suspected, and in the presence of prosthetic valve endocarditis. These criteria should identify those patients where the benefits obtained from cardiac catheterisation outweigh the increased risk of the procedure in infective endocarditis.

In patients with left ventricular failure caused by severe valvular disease the clinical findings along with echocardiography provide a satisfactory means of preoperative evaluation. Though our series of 18 patients is small and includes only patients with left sided endocarditis, our study indicates that echocardiography can provide valuable preoperative data when included with the total clinical assessment of the patient. This applies particularly to those cases where clinical and echocardiographic assessment suggest single valve involvement.

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Br Heart J 1982; **48:** 538–40

Preoperative echocardiographic diagnosis of anterior mitral valve leaflet fenestration associated with infective endocarditis

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SUMMARY Previously unreported echocardiographic findings are described of two cases with anterior mitral valve leaflet fenestration associated with infective endocarditis. M-mode echocardiograms demonstrated a periodic interruption in the echo tracing of the mitral valve ring area. Long axis real time two dimensional echocardiograms showed an echo defect in the body portion of the anterior mitral valve leaflet. Preoperative echocardiographic diagnosis was confirmed at surgery and echocardiographic findings correlated well with surgical findings.

The usefulness of echocardiography in detecting vegetations and torn chordae of mitral valve leaflets is well known.[1–4] We do not see, however, reports on the echocardiographic diagnosis of perforated mitral valve leaflets, which is also an important complication of infective endocarditis.[5] In this communication we describe our recent experience of two cases with perforated anterior mitral valve leaflet complicated by infective endocarditis.

Case 1

A 31 year old woman was referred for assessment of valvular disease. This patient had suffered from infective endocarditis at the age of 17 and was diagnosed as having mitral valve regurgitation three years later. Elective surgery was planned and echocardiography and angiography were performed before that.

M-mode echocardiograms showed a very dilated left atrium with an anteroposterior diameter of 64 mm and left ventricular end-systolic and end-diastolic diameters of 50 mm and 73 mm, respectively. Movements of both the ventricular septum and posterior left ventricular wall were increased. The echo from the body of the anterior mitral valve leaflet was interrupted in early diastole by a disappearance of the D–E slope of the echo tracing.

A long axis real time two dimensional echocardiogram showed an echo defect on the body portion of the anterior mitral valve leaflet, indicated by an arrow on Fig. 1A. With a slight lateral rotation of the transducer the echo defect increased its size to 10 mm. A small flap-like echo was observed near this defect and it moved into the left atrium in systole and into the left ventricular outflow tract in diastole.

A short axis real time two dimensional echocardiogram at the level of the left ventricular outflow tract visualised an echo defect of 8 mm at the lateral portion of the body of the anterior mitral valve leaflet (arrow in Fig. 1B). At operation a round fenestration of 16×12 mm in size was confirmed (Fig. 2). A pericardial patch was sutured and annuloplasty was performed. Postoperative long axis real time two dimensional echocardiograms no longer showed the echo defect, multiple layered echoes being recorded at the sutured portion of the defect instead.

Case 2

A 33 year old woman was known to have been a drug addict for years. After physical examination, combined aortic and mitral valve disease was suspected and the patient was referred for echocardiographic examination. M-mode echocardiogram showed a wide band-like echo at the aortic valve recording position. A periodic interruption was observed in the echo tracing of the mitral valve ring area. Long axis real time two dimensional echocardiograms showed a huge mass echo which ejected into the aorta in systole and receded into the left ventricular outflow tract in diastole (Fig. 3 A and B). In systole a defect was observed in the echo from the body portion of the anterior mitral valve

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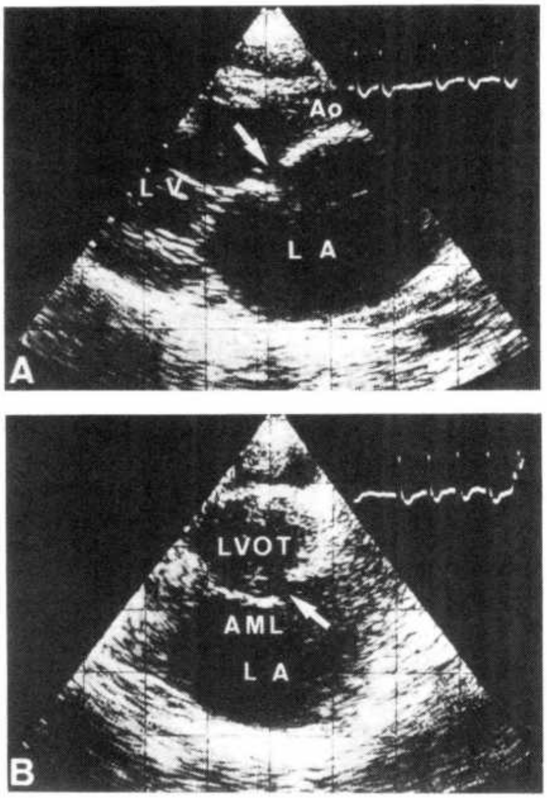

Fig. 1 *(A) A long axis real time two dimensional echocardiogram in systole showing a fenestration in the anterior mitral valve leaflet (arrow). Ao, aorta; LV, left ventricle; LA, left atrium. (B) A short axis real time two dimensional echocardiogram in systole showing a fenestration in the anterior mitral valve leaflet (arrow). LVOT, left ventricular outflow tract; AML, anterior mitral leaflet.*

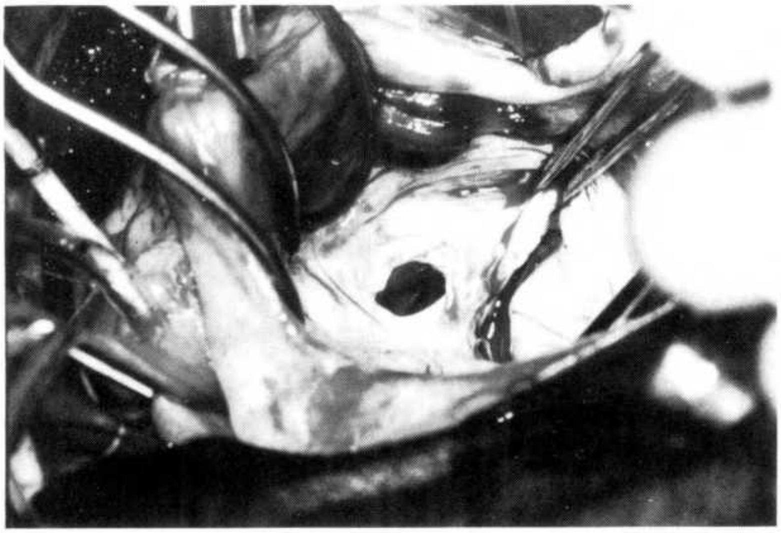

Fig. 2 *The operative finding of a fenestration in the anterior mitral valve leaflet viewed from the left atrium.*

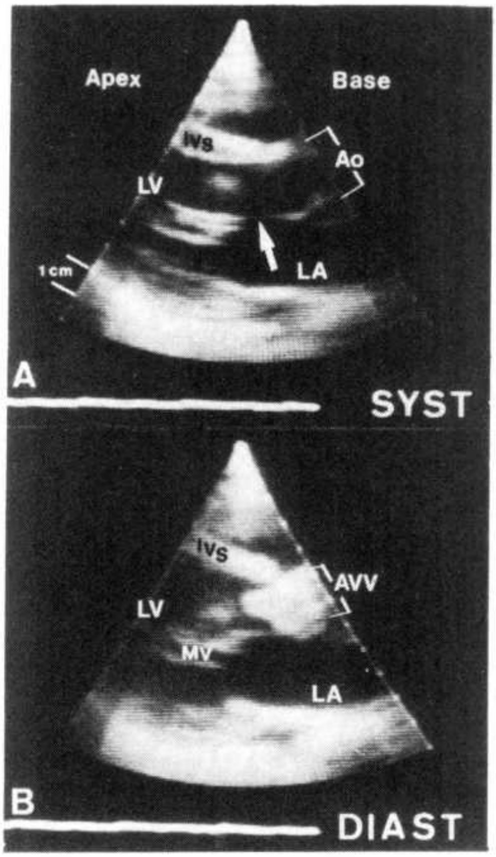

Fig. 3 *(A) Long axis real time two dimensional echocardiograms in systole (panel A) and diastole (panel B). The arrow in panel A indicates a tear in the body portion of the anterior mitral valve leaflet. In diastole the tear in the mitral valve leaflet is not recognisable because of the huge mass echo receding into the left ventricular outflow tract which is in contact with the tear. AVV, aortic valve vegetation; IVS, interventricular septum; MV, mitral valve. Other abbreviations as in Fig. 1.*

leaflet, but in diastole this defect was not recognisable because of the huge mass echo receding into the outflow tract. At operation a tear in the body of the anterior mitral valve leaflet resembling a fissure and a huge aortic valve vegetation were confirmed.

Comment

To our knowledge no reports have been published on echocardiographic features of mitral valve perforation resulting from infective endocarditis. Our two recent cases indicate that echocardiography can make this diagnosis.

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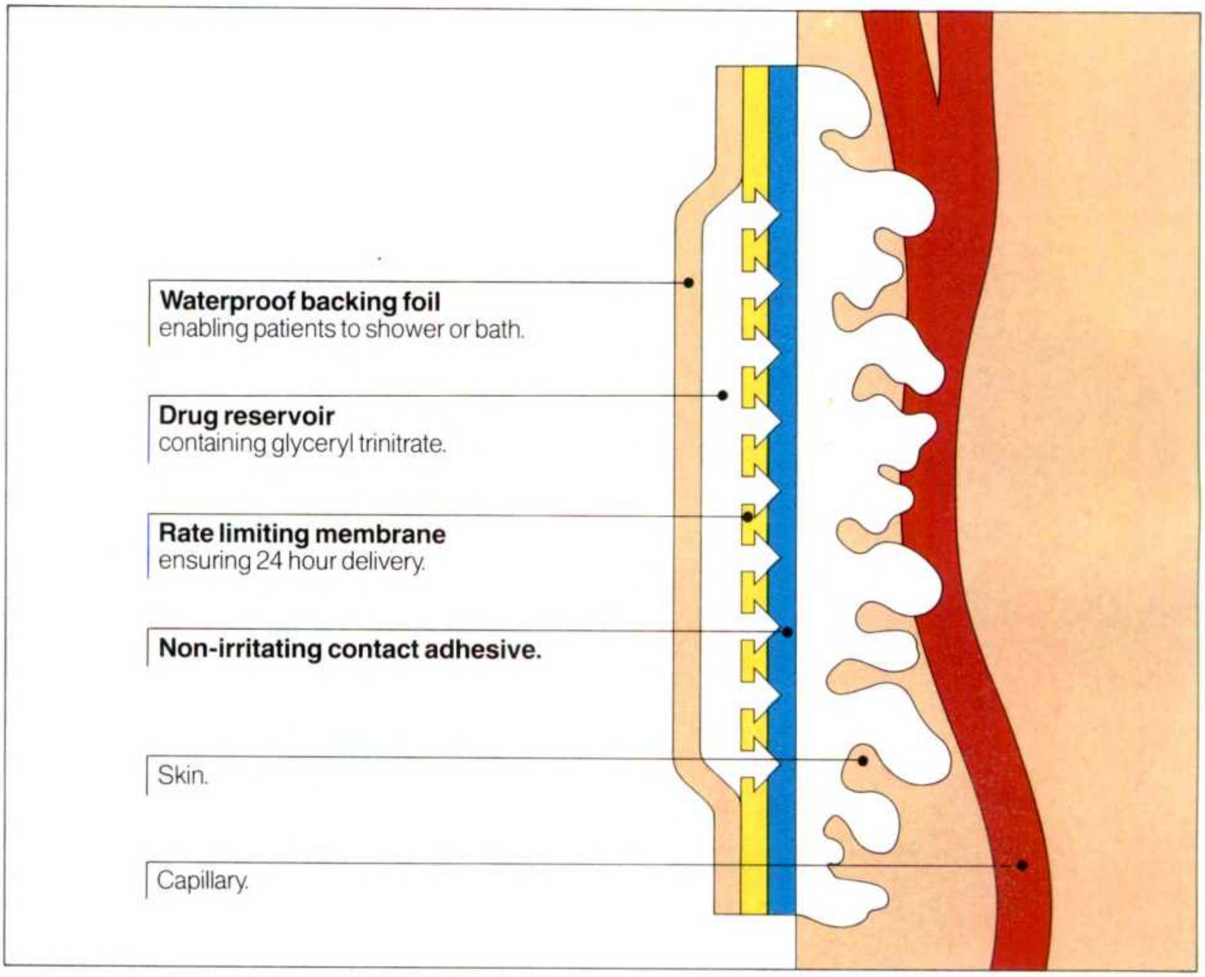
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Br Heart J 1982; **48**: 541–5

Haemodynamic and hormonal effects of captopril in primary pulmonary hypertension

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SUMMARY The treatment of primary pulmonary hypertension is unsatisfactory. Since, in animals, experimental pulmonary vasoconstriction may be mediated in part by angiotensin II, we treated five primary pulmonary hypertensive patients with captopril for four days. To ensure accuracy of haemodynamic and hormone data, the patients were studied under conditions of constant body posture, regulated dietary sodium and potassium intake, and unchanged diuretic therapy. Captopril reduced mean pulmonary arterial pressure in parallel with plasma angiotensin II levels. Right ventricular ejection fraction recordings increased considerably in three of four patients. Systemic arterial pressure fell, but there was no change in right atrial pressure, cardiac output, or heart rate. The decline in plasma (and urine) aldosterone levels presumably contributed to the positive cumulative potassium balance and the rise in plasma potassium (mean 0·7 mmol/l). These encouraging results suggest that converting enzyme inhibitors warrant a formal trial with prolonged follow up in the treatment of primary pulmonary hypertension.

Primary pulmonary hypertension is a chronic progressive disorder of unknown aetiology. With the exception of very rare cases who survive for long periods[1] or show regression,[2] most die within 10 years from the time of diagnosis.[3] No consistently effective treatment either curative or palliative has been discovered.

Animal studies have suggested firstly that the renin-angiotensin system may play a central role in the development of experimental pulmonary vasoconstriction,[4] and secondly that inhibition of angiotensin II formation can prevent the pulmonary vascular changes induced by chronic hypoxia.[5] The scant clinical data available indicate that converting-enzyme inhibitor therapy might prove beneficial in patients with raised pulmonary resistance.[6 7]

This communication presents detailed haemodynamic and hormone responses to the oral converting-enzyme inhibitor captopril in five patients with primary pulmonary hypertension.

Subjects and methods

Five patients (Table 1) with pulmonary hypertension were studied. All had formal diagnostic catheter studies previously to exclude left sided cardiac disease or intracardiac shunts. Four had no lung disease on respiratory function testing. One (case 4 Table 1) had evidence of small airways obstruction on computerised spirometry but no significant airways obstruction was demonstrable on routine spirometry. Informed consent was obtained from each patient, and the procedure was approved by the hospital ethical committee.

The study was carried out exactly as described earlier for patients with congestive heart failure.[8] In brief, a two day control period was followed by four days of captopril treatment; frusemide and digoxin, administered at 0800 h (Table 1) were continued unchanged; strict metabolic balance conditions were adhered to and dietary sodium (32 to 40 mmol/day) and potassium (50 to 98 mmol/day) were constant; urine was collected via an indwelling bladder catheter; haemodynamic recordings using a triple lumen Swan Ganz catheter and an arterial cannula were performed daily at 0830 h and 1530 h at which time arterial samples were drawn for hormone and electrolyte analysis as previously described.[8] Captopril was started after two control days at a dose of 6·25 mg, increasing to a maximum of 150 mg per dose by the penultimate study day. The drug was given three times daily, at exactly 0730 h, 1430 h, and 2330 h. Digoxin, frusemide, captopril, and potassium chloride (which was added to achieve a total potassium intake of 50 to 98 mmol/day) were the only drugs taken, any others

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Table 1 *Clinical and haemodynamic data*

		Case No.				
		1	*2*	*3*	*4*	*5*
Sex		F	M	M	M	F
Age		42	62	76	26	55
Duration of symptoms (y)		7	5	2	3	2
Mean pulmonary arterial pressure (mmHg)	Control	29	61·5	38	41	44·5
	Final day	26	53	32	33	37
Mean arterial pressure (mmHg)	Control	80	92	76	99	98
	Final day	63	73	51	82	77
Cardiac output (1/min)	Control	5·4	4·2	10·1	5·4	3·4
	Final day	6·6	3·7	9·3	6·0	3·1
Daily drugs		Frusemide 160 mg Digoxin 0·25 mg	Frusemide 40 mg	Frusemide 120 mg Digoxin 0·0625 mg	Frusemide 120 mg Digoxin 0·125 mg	Frusemide 40 mg

Data for pressures and cardiac output represent the mean of two recordings (0830 and 1530h) from the control (pre-captopril) day and from the final study day (during captopril treatment) for each patient.

having been stopped at least five days before starting the study.

In four patients, radionuclide ejection fractions of the right and left ventricles were determined by the first pass technique[9] using technetium-labelled pyrophosphate, firstly before the study, and again three to eight days after completion of the formal procedure during maintenance captopril treatment.

Our previous experience indicates that haemodynamic and hormone indices are often unstable on the first study day as the patients adjust to the procedure requirements and come into electrolyte balance on the controlled metabolic diet. To avoid spurious results therefore, data from the second day were taken as control (pre-captopril) values.

Statistical methods used were analysis of variance and product moment correlation coefficient. Results in the text and figure are presented as mean ± SEM.

Results

Clinical details, drugs, and pre-captopril pulmonary artery pressures are shown in Table 1.

HAEMODYNAMICS

Captopril induced highly significant decrements in arterial pressure and in pulmonary arterial pressure ($p < 0 \cdot 001$, analysis of variance) (Fig.). Mean arterial pressure reached its nadir 18·8 mmHg below baseline levels on the second day of captopril, whereas mean pulmonary artery pressure declined by 6·4 mmHg to its lowest level on the final study day (Fig.). A fall in pulmonary arterial pressure was seen in each patient, the initial (pre-captopril) level and those on the final day being shown in Table 1. Cardiac output changes were minor (Fig. 1 and Table 1) and were not statistically significant. Likewise, baseline right atrial pressure (8·4±1·9 mmHg, mean ± SEM) and initial heart rates (86·6±3·5 beats per minute) were not altered in any systematic fashion by captopril therapy. Since reliable measurements of pulmonary capillary wedge pressures are virtually impossible in pulmonary hypertension, and since extrapolation to left atrial pressure may be inaccurate,[10] pulmonary vascular "resistance" was not calculated. Right ventricular ejection fractions had increased conspicuously in three

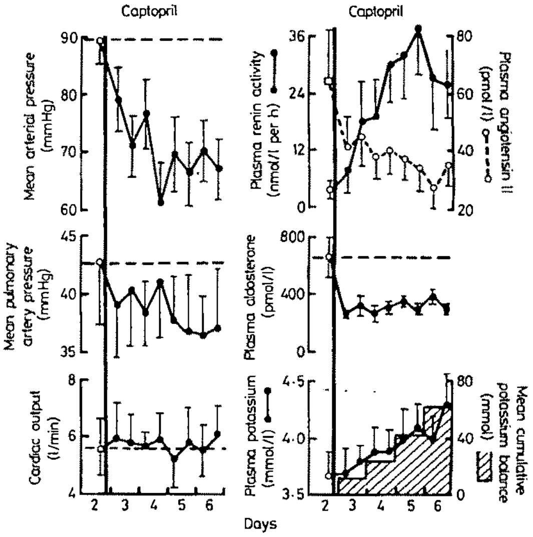

Fig. *Haemodynamic, hormone, and electrolyte results from five patients with primary pulmonary hypertension (mean ± SEM). Pre-captopril values (open symbols) represent the mean of two readings on the second study day, and are extended as discontinuous horizontal lines for the period of captopril treatment. Conversion to mass units: Plasma renin activity 1 nmol/l per h ≃ 1·3 ng/ml per h; Angiotensin II 1 pmol/l ≃ 1·04 pg/ml; Plasma aldosterone 1 nmol/l ≃ 36 ng/100 ml.*

Table 2 *Radionuclide ejection fractions before and after captopril*

Case No.	*Right ventricular ejection fraction*		*Left ventricular ejection fraction*	
	Before captopril	*After captopril*	*Before captopril*	*After captopril*
1	49%	67%	61%	80%
2	51%	43%	38%	46%
4	41%	89%	74%	84%
5	17%	40%	56%	80%
Mean	39·5%	59·8%	57·3%	72·5%

of the four patients three to eight days after completion of the study during continued captopril therapy, while left ventricular ejection fractions showed a more modest increment (Table 2).

HORMONES

Plasma angiotensin II fell steadily during captopril treatment, while plasma renin activity increased in a stepwise fashion to reach a peak on the penultimate study day which was tenfold higher than pre-captopril levels (Fig.). Plasma aldosterone declined rapidly and stabilised at approximately half baseline levels (Fig.). Overall, plasma aldosterone correlated significantly with concurrent plasma angiotensin II ($r=0{\cdot}53$, $p<0{\cdot}001$, $n=50$). Urine aldosterone excretion diminished gradually from a control of 38·4±6·2 nmol/24h to 29·2±2·8 nmol/24h on the final study day. Baseline levels of plasma noradrenaline 3570±727 pmol/l (604±123 pg/ml), plasma cortisol 469±64 nmol/l, and urine cortisol 275±19 nmol/24h and were not altered by the introduction of captopril.

HAEMODYNAMIC-HORMONE RELATIONS

The patterns of change in mean pulmonary artery pressure and in circulating angiotensin II were similar (Fig.). A possible relation between these two indices was supported by the close correlation between their concurrent mean values as plotted in the Fig. ($r=0{\cdot}91$, $p<0{\cdot}001$, $n=9$). The correlations of mean systemic arterial pressure with angiotensin II ($r=0{\cdot}69$, $n=9$) and with plasma renin activity ($r=-0{\cdot}83$, $n=9$) were also statistically significant ($p<0{\cdot}05$ and $p<0{\cdot}01$, respectively).

SODIUM AND POTASSIUM

Cumulative sodium balance in individual patients was variable during captopril administration, but overall was slightly negative (−24·4±19·3 mmol). By contrast, cumulative potassium balance was positive, and the mean plasma potassium increased by 0·7 mmol/l ($p<0{\cdot}001$, analysis of variance; Fig.) from a baseline level of 3·7 mmol/l (range 3·0–4·4 mmol/l).

CLINICAL STATUS

The two youngest patients (cases 1 and 4) noted a dramatic clinical improvement during maintenance captopril therapy. Exercise tolerance using a symptom-limited treadmill test[11] improved in case 1 from five minutes 12 seconds before captopril treatment to nine minutes five seconds after three weeks of treatment. Exercise performance was not assessed in case 4. His pulmonary arterial pressure, however, was measured using a Swan Ganz catheter after four months of treatment with captopril, and had declined to 41/13 mmHg from a pre-captopril level of 51/30 mmHg. Case 5 increased her exercise tolerance from nine minutes 30 seconds to 14 minutes nine seconds after four weeks of captopril, but has subsequently deteriorated clinically. Case 2, with the highest pulmonary pressure (Table 1), showed no change in exercise tolerance. Case 3 developed symptomatic hypotension, and thus captopril was withdrawn; he died three months later.

Discussion

The treatment of primary pulmonary hypertension is unsatisfactory. Though many drugs have been tried, none has proved uniformly effective. The rationale for the current study may be summarised as follows. In animals and man, angiotensin II can raise pulmonary arterial pressure independent of any action on the systemic arterial circulation.[12–14] Experimental pulmonary vasoconstriction secondary to hypoxia must be mediated by a vasoactive messenger, since the direct effect of low oxygen levels on pulmonary artery smooth muscle is one of dilatation.[15] Though contrary reports have appeared,[16] there is evidence that this hypoxia-induced pulmonary vasoconstriction in animals is angiotensin II-dependent,[4 5] and that blockade of angiotensin II formation by converting-enzyme inhibition can limit the development of pulmonary arterial hypertrophy and of right ventricular hypertrophy.[5]

The pathophysiological role of the renin angiotensin system in primary pulmonary hypertension in man is unknown and the effects of blocking angiotensin II formation in this condition have received scant attention. A single case study reported that captopril temporarily reduced dyspnoea and improved arterial oxygen tension,[7] and more recently Schmengler *et al.*[17] documented a decline in pulmonary arterial pressure after captopril treatment in 15 patients with pulmonary hypertension including five with primary pulmonary hypertension. Converting-enzyme inhibitor treatment decreased pulmonary arterial pressure and pulmonary vascular resistance in patients with systemic hypertension after coronary artery surgery.[6] Rich and Rosen,[18] however, failed to show a fall in four cases treated for 48 hours with captopril but noted great variability in the pressures over this period.

Our study shows that captopril is capable of causing a significant and sustained fall in pulmonary arterial pressure in primary pulmonary hypertension. The long period of study was designed to minimise the effect of short term fluctuations in pulmonary pressure as reported previously.[18] These patients were all suffering from pulmonary hypertension as evidenced by a resting mean pulmonary pressure clearly exceeding 25 mmHg in accordance with the WHO criteria for the diagnosis of pulmonary hypertension.[19] A mean pressure of 43 mmHg after 24 hours of bedrest represents at least a moderate grade of severity. The resting cardiac output was within the normal range, which is not unusual in cases of moderate severity on digitalis and diuretic treatment. They were all significantly limited on exercise. The important question is whether the modest fall in mean pulmonary pressure we observed was of clinical and haemodynamic benefit. Our data on exercise performance and right ventricular ejection fraction, though limited, indicate that it was. Right ventricular ejection fraction bears a close inverse relation to mean pulmonary arterial pressure.[20] Furthermore, a depressed ejection fraction indicates moderate or severe pulmonary hypertension, being normal in mild disease.[20] Ellis *et al.*[21] observed a significant increase in right ventricular ejection fraction with a fall in pulmonary pressure after low flow oxygen therapy in patients with obstruction airways disease. The changes in right ventricular ejection fraction in our cases are compatible with the thesis that captopril was producing a worthwhile relief of pulmonary vasoconstriction. Cardiac output at rest showed a gradual increase but did not attain statistical significance. This may be because of the study design which contrasts with the usual procedures for vasodilator studies which are all short-term acute interventions. Schmengler *et al.*[17] reported falls in pulmonary vascular resistance and right atrial pressure despite a rise in cardiac output, with a fall of 10 mmHg in the mean pulmonary pressure.

Left ventricular ejection fraction improved somewhat in our study though it was within the normal range in the initial diagnostic studies. We are unaware of any previous studies on the effect of vasodilator drugs on left ventricular ejection fraction in this condition. While left ventricular function may be grossly normal in pulmonary hypertension, detailed studies[22] have shown depressed contractility and limitation of the Frank-Starling mechanism because the pulmonary vascular changes impede left ventricular filling. The acute induction of pulmonary hypertension by hypoxia in animals is generally accompanied by a decrease in ejection fraction.[23] The study of Schmengler *et al.*[17] quoted previously also reported a fall in pulmonary wedge pressure with improvement in cardiac output with captopril, indicating improvement in left ventricular function. It is unlikely that the improvement in right ventricular performance in our patients was secondary to alterations in left ventricular function since the magnitude of change in ejection fraction was substantially greater for the right than for the left ventricle.

The close relation between mean pulmonary artery pressure and angiotensin II levels in our study suggests the possibility that the octapeptide was contributing to the pulmonary vasoconstriction. Support for this premise comes from data showing a close association of pretreatment renin levels with changes in pulmonary vascular resistance induced by converting-enzyme inhibitor therapy.[6 17] Whether long term captopril therapy results in a sustained lowering of pulmonary artery pressure, and if so whether it can be explained fully by the decline in circulating angiotensin II levels, remains to be determined.

The hormonal and metabolic changes were entirely predictable on the basis of converting-enzyme inhibition, that is a fall in angiotensin II and therefore in aldosterone, and a concomitant rise in plasma renin. Likewise, a positive cumulative potassium balance and increase in plasma potassium were not unexpected since similar changes were observed during captopril treatment for cardiac failure.[8] Presumably these potassium changes resulted in part from the decline in aldosterone levels.

The syndrome of primary pulmonary hypertension is not a homogeneous entity and several mechanisms, some as yet undiscovered, may be implicated. It is highly likely that some patients will either respond poorly or not at all to converting enzyme inhibitors. This has been the experience with other vasodilators in the treatment of primary pulmonary hypertension. Our data suggest that converting-enzyme inhibitors warrant a trial in individual patients where other forms of treatment have failed.

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Transmural, haemorrhagic myocardial infarction after intracoronary streptokinase

Clinical, angiographic, and necropsy findings

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SUMMARY Six of 101 patients with acute myocardial infarction whose coronary arteries were successfully recanalised died in cardiogenic shock one to 18 days after intracoronary thrombolysis. In one patient, cardiogenic shock was preceded by coronary artery reocclusion. On admission, serum creatine kinase was still normal in all six patients and there was significant ST elevation but no changes in the QRS complexes. Four of the six patients had an old infarct. The time between the onset of symptoms and coronary artery recanalisation was approximately 2·9 hours. The total dosage of intracoronary streptokinase averaged 200 000 units. Necropsy disclosed a patent vessel supplying the infarct in five patients and thrombotic reocclusion in the one patient with reinfarction. All six patients had a transmural acute myocardial infarction, which was typically anaemic in the two patients with inferior infarction. In one of these two patients, whose artery was recanalised within 1·7 hours, the anaemic infarct was only 4 cm^2 in area, whereas in the other (the patient who died after reocclusion) it was 30 cm^2. In three patients with an acute occlusion of the left anterior descending coronary artery, whose vessels were recanalised within 3·5 hours, the infarct was haemorrhagic and large, averaging 32 cm^2. Haemorrhage was always confined to the area of necrosis and there was no evidence of cardiac rupture. One other patient had both types of infarction—a large haemorrhagic infarct in the area of the recanalised circumflex coronary artery and an anaemic infarct in the area supplied by the severely stenosed left anterior descending coronary artery.

In this patient, who died 18 days after recanalisation, the speed of infarct healing was much delayed in the haemorrhagic but not in the anaemic infarct area.

Despite coronary artery recanalisation within three and a half hours, a fatal transmural acute myocardial infarction with reperfusion haemorrhage into the area of necrosis may occur. Myocardial haemorrhage probably delays infarct healing.

During the past three years, we have successfully recanalised the coronary arteries of 101 patients with an acute transmural myocardial infarction using intracoronary streptokinase. Six of the 101 patients died in cardiogenic shock one to 18 days after the procedure. Death was preceded by reinfarction caused by coronary artery reocclusion in only one patient. In all six patients, necropsy was performed in order to assess infarct size objectively and to differentiate an anaemic from a haemorrhagic infarct. Experimentally, haemorrhagic infarction has been observed after myocardial reperfusion, and from systemic streptokinase treatment it is known that myocardial haemorrhage also occurs in man.[1] In this paper, the necropsy findings of the six patients are summarised and related to clinical and angiographic data.

Methods

CLINICAL CHARACTERISTICS ON ADMISSION

According to our procedure, the duration of chest pain was less than three hours in all six patients. One patient was already in the hospital when the infarct occurred; another was working at the hospital when his chest pain began. On admission, all six patients were in left ventricular failure. Arterial blood pressure, however,

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was still within the normal range. Four patients had a history of an old transmural myocardial infarction. The electrocardiogram showed distinct ST elevation, with no evidence of new Q waves. Serum creatine kinase was within normal limits, confirming the early stage of the infarct.

RECANALISATION AND POST-THROMBOLYTIC TREATMENT

Coronary artery recanalisation was performed as described by us previously.[2] First, the "infarct vessel" was recanalised, then the non-affected coronary artery and the left ventricle were visualised. In one patient, streptokinase was given superselectively through a 3 French reperfusion catheter, which was advanced through an 8 French Judkins right coronary artery catheter up to the thrombus. In another patient, where streptokinase had transformed a total into a subtotal occlusion, intracoronary lysis was followed by balloon dilatation using a Grüntzig dilatation catheter DG 20-30.

Five of the six patients were still in the intensive care unit when they died. The patient with reinfarction was in the general ward and was readmitted to the intensive care unit; she died two days later. All patients received intravenous heparin and, as long as their blood pressure permitted, they also received intravenous glyceryl trinitrate (50 mg daily) and oral nifedipine (20 mg four times daily), in order to prevent coronary artery reocclusion from spasm. Haemodynamic variables were monitored with a Swan-Ganz catheter and medical treatment was administered according to these measurements. When left ventricular failure worsened, the patients were intubated and artificially ventilated.

NECROPSY

The necropsies were performed 24 to 30 hours after death. The hearts were weighed and examined according to a routine procedure. First, the coronary arteries were carefully prepared and dissected, in order to identify the exact location and extent of the atheromatous stenoses and thromboses. Second, the chambers were opened and the degree of dilatation was measured and recorded, together with other qualitative changes, such as subendocardial bleeding or parietal thrombosis. Third, horizontal sections were cut through the anterior wall of the left ventricle as well as the interventricular septum and the inferior left ventricular wall. On these cut surfaces the size and the quality of the infarct were assessed. For histological evaluation, two or three specimens were taken from the centre of the infarct, from the margin, and from the non-infarcted myocardium.

Results

ANGIOGRAPHIC FINDINGS

Coronary angiography disclosed three vessel disease in all six patients. The "infarct vessel" was completely occluded. It was recanalised by a streptokinase infusion into the ostium of the right or left coronary artery in four patients, a superselective streptokinase infusion in one patient, and a streptokinase infusion followed by balloon dilatation in the remaining patient. The average streptokinase dosage was 200 000±25 000 units. The time interval from the onset of chest pain to recanalisation was 2·9±0·8 hours, ranging from 1·7 to 3·5 hours (Table). A significant arteriosclerotic stenosis always remained after recanalisation, but there was good and prompt contrast filling of the previously occluded artery. Angiographically, there was no evidence of preformed collaterals to the "infarct vessel" in any of the six patients. The left ventricular ejection fraction immediately after recanalisation was conspicuously reduced to 26±8%.

CLINICAL COURSE AFTER RECANALISATION

In case 1, recanalisation was associated with distinct clinical improvement and the reversal of impending shock. Nine days after recanalisation, however, reinfarction occurred as evidenced by typical ischaemic chest pain, ST re-elevation, and a rise in serum creatine kinase. A second attempt to recanalise the reoccluded

Table *Summary of clinical, angiographic, and necropsy data*

Case No:	*Sex*	*Age (y)*	*AMI*	*Old MI*	*Infarct vessel*	*Intracoronary streptokinase (units)*	*Chest pain to reperfusion (hours)*	*Peak serum CK (U/l)*	*AMI to death (d)*	*Coronary artery reocclusion*	*AMI area* (cm^2)	*Myocardial haemorrhage*
1	F	71	I	A	RCA	175 000	2·0	428	9	+	30	–
2	M	70	I	A	RCA	200 000	1·7	250	2	–	4	–
3	M	69	A	I	LAD	190 000	3·5	1968	1	–	30	+
4	F	77	A	—	LAD	190 000	3·4	3350	3	–	24	+
5	M	72	A	I	LAD	250 000	3·5	4000	1	–	42	+
6	M	44	I(+A)	—	Cfx (+LAD)	200 000	3·0	3100	18	–	99	+(–)

AMI, acute myocardial infarction; MI myocardial infarction; I, inferior; A, anterior; RCA, right coronary artery; LAD, left anterior descending coronary artery; Cfx, circumflex coronary artery.

proximal right coronary artery with streptokinase was unsuccessful and the patient died in cardiogenic shock.

In cases 2 to 6, left ventricular failure persisted after recanalisation. These five patients required increasing dosages of positive inotropic agents to maintain their arterial pressure. There was no evidence of reinfarction before death in these five patients. They all died in cardiogenic shock.

Serum creatine kinase rose rapidly after recanalisation. Peak serum creatine kinase in cases 1 and 2 was 428 and 250 units/l, respectively, and in cases 3 to 6 peak creatine kinase averaged 3104±847 units/l (Table). New Q waves appeared in all six patients after recanalisation.

NECROPSY FINDINGS WITH RESPECT TO RECANALISATION

Necropsy disclosed a patent "infarct vessel" in cases 2 to 6 and an acute thrombotic reocclusion in case 1 with reinfarction. At the sites where thrombotic occlusions had been detected by angiography before recanalisation, the coronary arteries showed severe arteriosclerotic stenoses.

All six patients had a transmural infarct (Table). In cases 1 and 2, with inferior infarctions, the infarct was typically anaemic; their sizes were 30 cm^2 and 4 cm^2, respectively. Both patients had an old anterior infarct and in both recanalisation was achieved in less than two hours after the onset of chest pain. There was discrete involvement of the right ventricle in case 1.

In cases 3 to 5, with acute occlusion of the left anterior descending coronary arteries, the "infarct vessel" was opened within three and a half hours after the onset of chest pain. Necropsy showed large transmural infarcts averaging 32±9 cm^2 in area. The infarcts were almost completely haemorrhagic, leaving only a small anaemic border zone. Haemorrhage was always confined to the area of necrosis with no evidence of cardiac rupture. A typical example is shown in Fig. 1. Histologically, the haemorrhagic infarct was characterised by eosinophilic coagulation necrosis of the myocardial fibres. This was accompanied by intensive fresh haemorrhage between the myofibres (Fig. 2a). A neutrophilic exudation was almost absent. The wall of the small arterial vessels also appeared to be necrotic (Fig. 2b).

Case 6, who died 18 days after recanalisation, had a haemorrhagic infarct in the area supplied by the occluded and recanalised circumflex coronary artery and an anaemic infarct in the area supplied by the severely stenosed left anterior descending coronary artery (Fig. 3). Streptokinase had been infused into the left main coronary artery in this patient. According to the single peak in serum creatine kinase and the infarct age estimated on the basis of the gross and microscopical changes, the anterior anaemic infarct probably occurred at the same time as the posterolateral haemorrhagic infarct. Since this patient died 18 days after recanalisation, histological samples from the anaemic and haemorrhagic infarct areas were examined with special regard to the question whether the speed of infarct healing was affected by myocardial haemorrhage. Fig. 4 shows a specimen from the margin of the anaemic infarct directly adjacent to the haemorrhagic infarct. The area of the anaemic infarct shows signs of advanced repair with granulation tissue almost completely replacing the necrotic muscle fibres. In contrast, the area of the haemorrhagic infarct showed no signs of repair.

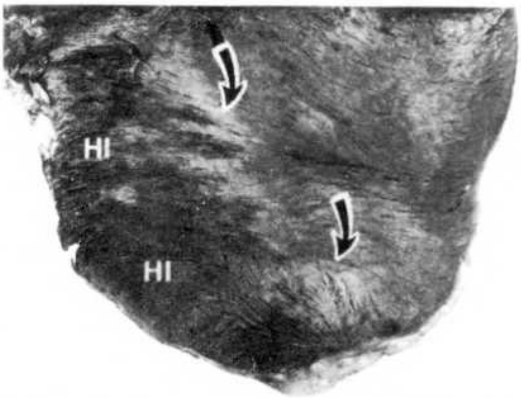

Fig. 1 *Horizontal cut surface of the septum and the posterior wall of the left ventricle with acute haemorrhagic infarct (HI) affecting almost the entire interventricular septum (case 5). Anaemic margin (arrows).*

Discussion

The clinicopathological observations described in this paper are the first obtained in patients who have had intracoronary streptokinase treatment. It is the nature of such data that they are "negative" and selective.

Clinically and angiographically, our six patients did not recognisably differ from many other patients undergoing coronary artery recanalisation, with the exception that their left ventricular ejection fraction was so depressed. All six patients had recanalisation within the time limit at present considered to be appropriate for patients with acute myocardial infarction.[2-4] The normal serum creatine kinase levels on admission and the acute electrocardiographic findings make it unlikely that the onset of coronary artery occlusion was significantly different from the onset of chest pain in these patients.

In cases 1 and 2, coronary artery reperfusion was achieved within two hours after the onset of chest pain. It may have salvaged ischaemic myocardium in case 2,

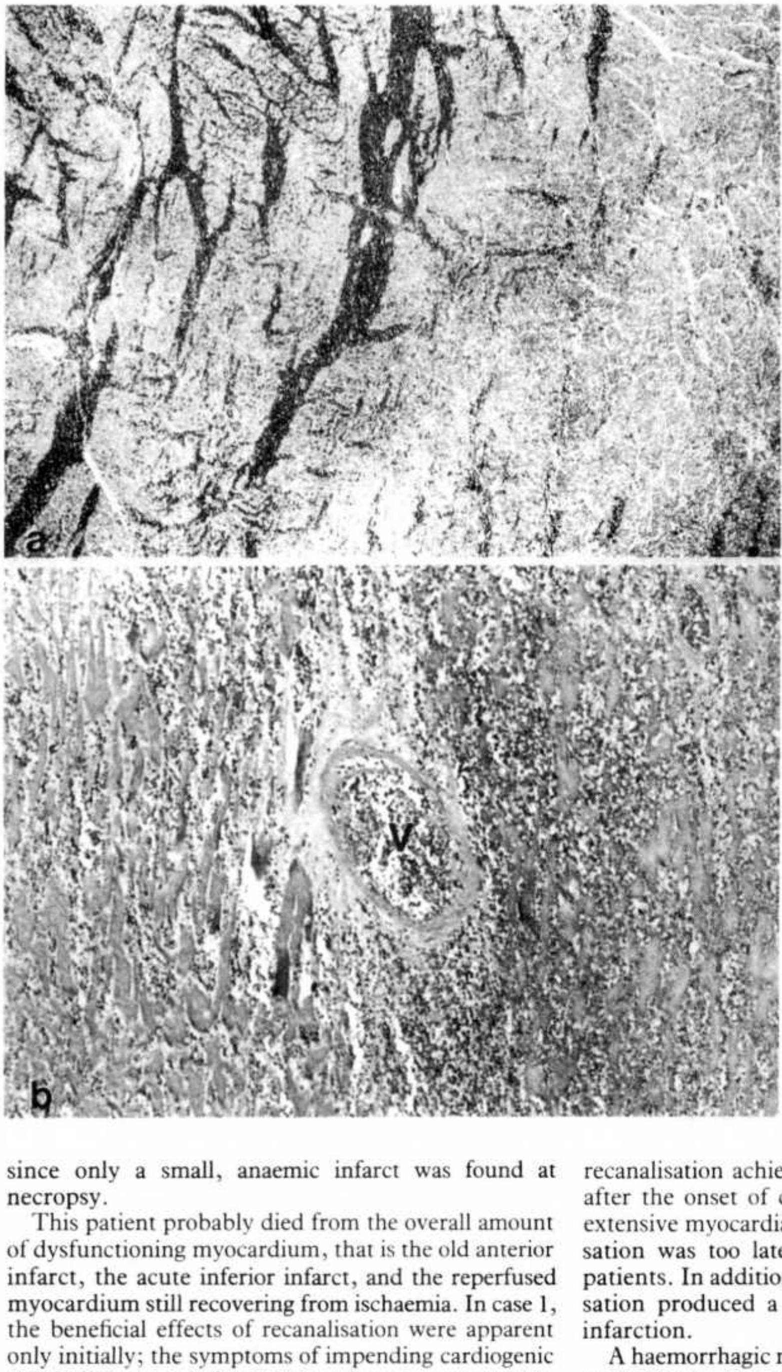

Fig. 2 *Acute haemorrhagic infarction. (a) Low power micrograph showing interconnecting strands of erythrocytes between myofibres. (HE × 40, original magnification.) (b) High power micrograph displaying massive haemorrhage between necrotic myofibres. In the centre a small vessel (V) with necrotic wall. (HE × 115, original magnification.)*

since only a small, anaemic infarct was found at necropsy.

This patient probably died from the overall amount of dysfunctioning myocardium, that is the old anterior infarct, the acute inferior infarct, and the reperfused myocardium still recovering from ischaemia. In case 1, the beneficial effects of recanalisation were apparent only initially; the symptoms of impending cardiogenic shock disappeared. Reocclusion, however, resulted in reinfarction and irreversible shock. Thus, the beneficial effect of coronary artery recanalisation could not be sustained in this patient. In cases 3 to 6, the clinical course and the necropsy findings indicate that recanalisation achieved within three and a half hours after the onset of chest pain did not prevent a fatal extensive myocardial infarction. Apparently, recanalisation was too late to salvage myocardium in these patients. In addition, there is little doubt that recanalisation produced a haemorrhagic type of myocardial infarction.

A haemorrhagic myocardial infarction is rarely seen. Reviewing our last 200 necropsies of patients who died after an acute myocardial infarction, no haemorrhagic infarct was found even in five patients who received intracoronary streptokinase but in whom the "infarct vessel" was not reopened. Myocardial haemorrhage

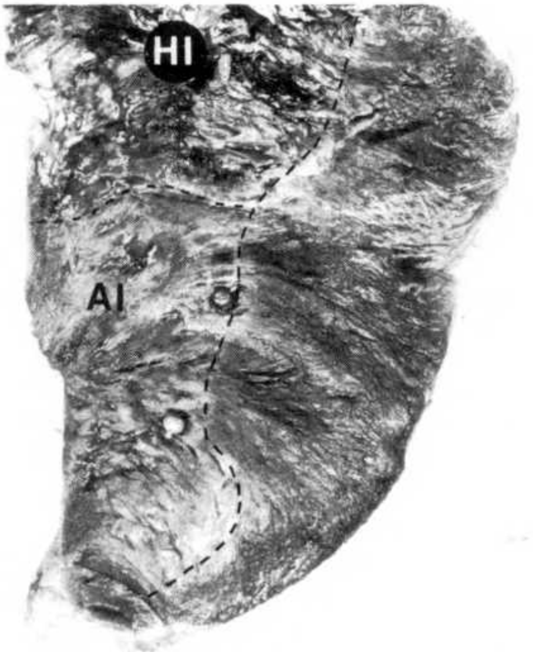

Fig. 3 *Horizontal cut surface of the anterior wall of the left ventricle with an 18 day old haemorrhagic infarct (HI) at the basis (case 6). Close by, an anaemic infarct (AI) of equal age.*

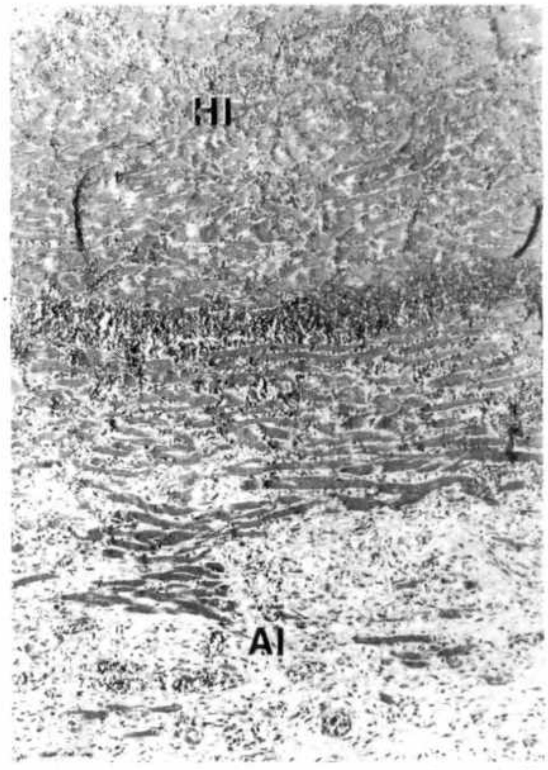

Fig. 4 *Anaemic infarct (AI) in repair (case 6), characterised by granulation tissue, adjacent to a haemorrhagic infarct (HI) of the same age without any evidence of repair. (HE × 115, original magnification.)*

has been described after systematic streptokinase. Since it is also observed after experimental reperfusion and occasionally after coronary artery bypass in patients with acute myocardial infarction,[5] however, it may not be the result of streptokinase *per se*, but the consequence of early myocardial reperfusion after intracoronary thrombolysis. The findings in our last patient (case 6) would be consistent with this hypothesis. This patient had a haemorrhagic and an anaemic infarct of equal age. The haemorrhagic infarct occurred only in the area of the totally occluded and recanalised coronary artery, whereas the anaemic infarct occurred in the area of the severely stenosed left anterior descending coronary artery, where no reperfusion took place. Thus, sudden reperfusion after three to four hours of coronary artery occlusion appears to be a major determinant in the development of myocardial haemorrhage. The anaemic anterior infarct in this patient may have been caused by a drop in perfusion pressure and/or loss in collateral blood flow from the acutely occluded circumflex coronary artery to the left anterior descending coronary artery. Since this patient died 18 days after recanalisation and had both types of infarction, it was interesting to see how the speed of healing of the acute infarct was affected by myocardial haemorrhage. The histological specimens from this patient showed a clear-cut difference in the removal of necrotic muscle and replacement by connective tissue between the anaemic and the haemorrhagic infarct. While in the haemorrhagic infarct area, repair processes were completely lacking after 18 days, the anaemic infarct showed the typical picture of an infarct in resorption and repair by granulation tissue. Obviously, myocardial haemorrhage delayed infarct healing in this patient. In case 4, who died three days after an acute anterior infarct, the expected degree of leucocytic infiltration was also not seen.

Thus, our findings show that a large fatal infarct may occur despite recanalisation within three and a half hours after the onset of chest pain. They also suggest that myocardial haemorrhage is likely to follow coronary artery reperfusion, thereby possibly delaying the speed of infarct healing.

Although we cannot be certain that a haemorrhagic infarct similar to that in cases 3 to 6 is not present in many patients undergoing recanalisation and surviving the acute infarct, we have continued to undertake this procedure. A substantial improvement in regional wall motion after successful thrombolysis[6] in connection with a reduction in thallium-201 defect size in the majority of patients, as well as distinct haemodynamic improvement in some patients with cardiogenic shock[7] has encouraged us. We attempt, however, to recanalise patients with an extensive anterior infarct as early as possible with a strict limit on the acceptable duration of symptoms of three hours. Otherwise, instead of a reduction in infarct size, myocardial haemorrhage is likely to be induced, thereby possibly disturbing infarct healing. We are aware that a large interindividual variation in the development of a complete myocardial infarction exists.

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Sudden versus gradual withdrawal of sotalol in ambulant patients with ischaemic heart disease

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SUMMARY One hundred and six patients with ischaemic heart disease on chronic treatment with sotalol or placebo were asked to discontinue the drugs gradually or abruptly. Even though the patients were fully active at home there was a very low incidence of major cardiac events but a significant worsening of anginal symptoms in patients previously taking sotalol. The rate at which the sotalol was discontinued did not appear to be important.

Concern about a beta blocker withdrawal rebound phenomenon continues. Numerous case reports[1–9] of major cardiac events occurring after the sudden discontinuation of these drugs in patients with ischaemic heart disease seem to support the idea of rebound, but in a condition as unpredictable as coronary heart disease the value of this evidence is open to question. Four retrospective studies[10–13] failed to confirm clinically significant rebound and a recent prospective study of patients with angina admitted to hospital[14] showed a low incidence of cardiac events after the sudden discontinuation of propranolol.

In this study an attempt has been made to evaluate the risk of sudden withdrawal of sotalol in patients with coronary heart disease who were all fully ambulant at home.

Subjects and method

The patients formed part of a larger sotalol secondary prevention trial, the details of which can be found elsewhere.[15] All had had a definite acute myocardial infarction and had been randomly allocated on a 3:2 basis within 14 days of infarction to sotalol (320 mg daily) or placebo. The first 106 patients to complete 12 months follow-up were enrolled in this study, and were randomly allocated on a 1:1 basis to either gradual (over two weeks) or abrupt (immediate discontinuation) withdrawal of the trial drug. The groups were well matched with regard to age, sex, pre-existing hypertension, pre-existing angina, smoking habits, and site of infarction. All patients were fully ambulant at home and 38 were working. On entry into this study renal function (as reflected by blood urea) and nitrate therapy were recorded. Four weeks after stopping the trial drug the patients were assessed by a doctor blind to both randomisations. During the 12 month period of treatment and the one month period after drug withdrawal all antianginal agents except nitrates were prohibited.

Results

The distribution of patients was: 44 on placebo; 31 gradual withdrawal from sotalol, and 31 abrupt withdrawal from sotalol.

MAJOR CARDIAC EVENTS

This heading includes sudden death, major arrhythmias, fatal and non-fatal myocardial infarction, and severe angina requiring hospital admission.

The only major cardiac event was a non-fatal myocardial infarction complicated by ventricular fibrillation in a patient who had stopped sotalol after gradual withdrawal.

ANGINA (Table)

In the placebo group 17 patients experienced angina while taking the trial drug. Three felt the angina to be worse after stopping the drug while one felt improved. None developed new onset angina or had a recurrence of previous angina. In the group who gradually stopped sotalol 12 had angina while taking the drug and all continued to have it afterwards. Six felt unchanged after stopping but six felt worsening of the angina though none required admission to hospital. One developed new onset angina and two had a recurrence of previous angina.

In the group who suddenly stopped sotalol 16 had angina while taking the drug and all experienced

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Table *Effect of withdrawing treatment on angina*

	Placebo (44)	*Sotalol (gradual withdrawal) (31)*	*Sotalol (abrupt withdrawal) (31)*
Angina during treatment	17 (39%)	12 (39%)	16 (52%)
Angina worse after stopping treatment	3 (7%)	6 (19%)	7 (23%)
Angina unchanged after stopping treatment	13 (30%)	6 (19%)	8 (25%)
Angina improved after stopping treatment	1 (2%)	0	1 (3%)
New onset angina after stopping treatment	0	1 (3%)	2 (6%)
Recurrence of angina after stopping treatment	0	2 (6%)	0

angina after stopping. Eight felt unchanged, seven had worsening of the angina, and one felt improved. Two patients developed new onset angina but none had a recurrence of previous angina. None required hospital admission.

PALPITATION

Several patients reported an unusual awareness of their heart beat during the study. In the placebo group three had palpitation while on treatment and all continued to experience it after stopping the drug. One developed palpitation for the first time after discontinuation of the trial drug. In the sotalol group on gradual withdrawal none had palpitation on treatment but four developed it after stopping, while in the abrupt withdrawal group one had palpitation on treatment and continued to suffer it after stopping, while four developed new onset palpitation after stopping.

GENERAL WELL-BEING

In the placebo group, three patients felt better and four felt worse after stopping treatment, while in the sotalol groups two patients felt better and two felt worse after gradual withdrawal and one felt worse after abrupt withdrawal.

HEART RATE

The mean heart rate of the placebo group on treatment was 69 beats/minute and after stopping 72 beats/minute. In the sotalol group on treatment the mean heart rate was 57 beats/minute which was significantly slower than the placebo group ($p<0{\cdot}01$). The mean heart rate after stopping sotalol rose to 81 beats/minute in the gradual withdrawal group and to 82 beats/minute in the abrupt withdrawal group which was significantly faster than while on sotalol ($p<0{\cdot}01$) and compared with patients who discontinued placebo ($p<0{\cdot}01$).

BLOOD PRESSURE

The mean blood pressure in the placebo group was 150/90 mmHg on treatment and 152/92 mmHg after stopping. The mean blood pressure in the sotalol group was 145/89 mmHg, and after stopping the drug 145/89 mmHg after gradual withdrawal and 146/89 mmHg following abrupt withdrawal. Eleven patients in the sotalol group had a history of hypertension and of these only two showed a large rise in blood pressure after stopping the drug. The patient who had the largest rise from 140/100 to 180/120 mmHg suffered the only myocardial infarction in the series.

RENAL FUNCTION

There was no difference in renal function as judged by blood urea measured immediately before discontinuing the trial drug.

Mean Urea. (a) Placebo group 6·1 mmol/l (range 2·6–8·6); (b) sotalol (gradual withdrawal) 5·4 mmol/l (range 3·1–9·4); (c) sotalol (abrupt withdrawal) 5·4 mmol/l (range 2·8–9·5).

NITRATE TREATMENT

Patients were allowed glyceryl trinitrate as required. At the start of this study only six were using long acting nitrates: one in the placebo group, two gradually stopping sotalol, and three abruptly stopping sotalol. None was using any other antianginal drug.

Discussion

It is important to distinguish between the effects of sotalol withdrawal compared with placebo from the effects of withdrawing sotalol gradually or suddenly. As sotalol is an effective antianginal drug, one might anticipate worsening of angina after its withdrawal. This is the case in our study where only 7% of the placebo group experienced worsening of angina after stopping the drug compared with 21% of patients who stopped sotalol (SE 6·4). There was no difference in the incidence of worsening angina between the patients suddenly stopping (23%) and those gradually stopping sotalol (19%). New onset angina was uncommon but was confined to patients discontinuing sotalol. Though this might be a rebound phenomenon a likely explanation is progression of the coronary heart disease, the clinical expression of which had been prevented by sotalol. Similarly the reappearance of previous angina may reflect simply the removal of effective suppressive treatment. The rate of sotalol withdrawal did not influence the incidence of new onset or recurrent angina.

The incidence of major cardiac events was very low even in patients who were fully active at home or at work. The single non-fatal myocardial infarction occurred in a patient who had stopped sotalol after gradual withdrawal. This individual was previously hypertensive and showed a large increase in blood pressure after stopping sotalol. This reaction, however, appeared to be uncommon and occurred in only two of the 11 hypertensive patients treated with sotalol.

Patients taking sotalol had a significant bradycardia, and interestingly after stopping the drug appeared to have a slight overshoot in their mean heart rate which exceeded that of the placebo group (82 beats/minute and 72 beats/minute, respectively). The rate of sotalol withdrawal did not appear to influence the mean heart rate. Whether this represents a change in catecholamine levels or increased sensitivity of the beta receptors as suggested by Boudoulas *et al.*[16] is not clear. Whatever the mechanism underlying the overswing, it appears to be of no clinical significance. With regard to minor symptoms there was no real difference in the general well-being between patients in any of the groups after withdrawal of treatment except for palpitation which was experienced more frequently by those discontinuing sotalol.

This study shows that sotalol can be discontinued in patients with ischaemic heart disease who are fully active at home without major risk of a cardiac catastrophe. It is however important to anticipate worsening of angina in some patients simply on the basis of withdrawing an effective antianginal agent. Whether sotalol was discontinued gradually or suddenly appeared unimportant. Before concluding that beta blockers in general can be safely stopped in a sudden fashion, however, one must consider the half life of the particular drug. Sotalol has a long half life (seven to 18 hours) so even sudden discontinuation of treatment may still allow a relatively gradual reduction in beta blockade compared, for example, with the discontinuation of a short acting drug such as propranolol. Though the results of this study must be interpreted in the context of a long half life beta blocker the precise clinical importance of half life duration remains unclear. The study of Myers *et al.*[14] of propranolol withdrawal in patients in hospital suggests even short half life beta blockers can be suddenly stopped without major risk.

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Projection of ST segment changes on to the front of the chest

Practical implications for exercise testing and ambulatory monitoring

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SUMMARY In order to determine the optimal chest leads for exercise testing and ambulatory monitoring we have studied the projection of ST segment alterations on to the front of the chest in 200 patients. In 20 of these patients recordings during exercise were analysed to study the pattern of changes of the ST segment during and after exercise. The electrocardiogram was recorded using 16 unipolar chest leads equally spaced over the left hemithorax. ST segment elevation and depression projected to the front of the chest in a pattern that was individual to each patient and indeed the standard chest leads of the 12 lead electrocardiogram were seen to represent only 41% of the total projection. ST segment depression was usually first recorded in one or two leads and the number of leads involved increased as exercise progressed, returning to normal after exercise in a reciprocal fashion; the leads that first showed ST segment depression were almost invariably those with the most severe depression and the last in which it disappeared. Analysis of the precordial projection of the ST segment has allowed a 12 lead precordial matrix to be designed that can be recorded using a standard three channel electrocardiographic machine. This will provide important directional information about the severity of myocardial ischaemia when assessing the effects of interventions that would not otherwise be available using conventional electrocardiographic lead systems. It is also clear from these data that failure to record ST segment changes using ambulatory monitoring in patients complaining of chest pain may mean that the wrong site was selected for placing the exploring electrode. Moving one or both of the exploring electrodes to other positions of the precordial matrix in subsequent recordings may then provide diagnostic information that otherwise would have been missed.

In recent years there has been increasing interest in the use of non-invasive tests to diagnose and evaluate patients with ischaemic heart disease. Exercise testing has proved to be the most useful and widely available technique and more recently 24 hour ambulatory monitoring of ST segments has provided a means of evaluating patients in their everyday life.[1–3] Initially only a single chest lead was used for exercise testing and many limitations of the technique were resolved by using the standard 12 lead electrocardiogram.[4] More recently we and others have found it more useful to use a 16 lead precordial mapping system for both the diagnosis and the evaluation of patients with ischaemic heart disease.[5–7] In spite of a vast amount of research on the value of exercise testing in identifying coronary artery disease there has been little work describing the pattern of ST segment projection on to the front of the chest during an exercise test. Without this information many of the strengths and weaknesses of exercise testing and ambulatory monitoring will remain speculative.

Methods

PATIENTS

Two hundred consecutive patients (170 men, 30 women) undergoing diagnostic coronary angiography were studied. One hundred and eighty two patients presented with chest pain. There were 18 patients without chest pain in whom the angiograms were performed for diagnostic purposes. They were aged 29 to 69 (mean 48·2±8·6) years.

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PRECORDIAL ELECTROCARDIOGRAPHIC MAPPING

All patients underwent 16 lead precordial electrocardiographic mapping before, immediately after exercise, and 10 minutes after exercise using a technique previously described.[5] The 16 points were distributed evenly over the left hemithorax and the boundaries were the angle of Louis, the right sternoclavicular joint, the posterior axillary line, and 6 cm below the xiphisternum (Fig. 1). The leads were unipolar chest leads connected via a Wilson central terminal. Graded maximal exercise tests were performed using a bicycle ergometer. Patients cycled at a constant speed (50 revolutions per minute) and the work load was increased by 25 watts each minute. The exercise tests were limited by the appearance of chest pain, dyspnoea, fatigue, and multiple ventricular ectopic complexes.

In 20 of the patients with proven coronary disease and ST segment depression, 16 lead precordial maps were recorded each minute during exercise.

INTERPRETATION OF RECORDS

At each of the 16 positions ST segment depression and elevation were measured in three complexes and an average taken. ST segment depression was measured in millimetres (mm) to the nearest 0·5 mm. The ST segment was considered depressed if there was a change of 1 mm or more lasting 0·08 s or longer. The ST segment was considered elevated if there was a change of 1 mm or more measured 0·06 s after the end of the QRS complex.

One of the precordial positions (C3) corresponded exactly to V5 and five of the 16 precordial leads (A2, B2, B3, C3, D3) covered the positions usually occupied by the chest leads of the standard 12 lead electrocardiogram (modified standard leads).[8] All data from the exercise tests were reported before the coronary arteriograms were obtained.

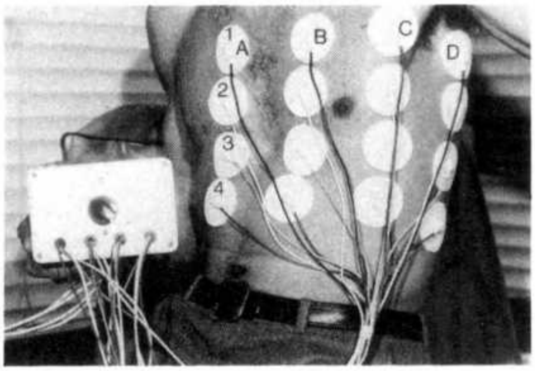

Fig. 1 *The electrodes are distributed over the left hemithorax and labelled A to D (vertical rows) and 1 to 4 (horizontal rows).*

CORONARY ARTERIOGRAPHY

All patients had left ventricular angiograms and coronary arteriograms performed using the Judkins technique. Coronary arterial narrowing was considered significant where the luminal diameter was decreased by at least 70%.

Results

Satisfactory recordings were obtained in all patients. The results of exercise testing and coronary arteriography are shown in Table 1. ST segment depression was found to occur in 122 of the 154 patients with coronary disease. A further 12 patients developed ST segment elevation alone.

Projection of ST segment depression to the 16 precordial leads is shown in Table 2. ST segment depression following exercise was projected to all 16 leads. ST segment depression was frequently recorded outside both V5 and the modified standard chest leads. Indeed ST segment depression recorded in the standard precordial leads represented only 41% of the total projection to the full 16 leads.

ST segment depression occurred exclusively outside the conventional precordial leads in nine of the 122 (7%) patients who developed ST segment depression and had coronary disease. Maximum ST segment depression occurred outside the conventional leads in 38 (31%) patients. In 21 (17%) patients ST segment depression was recorded outside the two leads (V5 and inferior) used for ambulatory monitoring.

Projection of ST segment elevation to the 16 precordial leads is shown in Table 3. Again ST segment elevation

Table 1 *Clinical details*

Exercise testing	
(A) ST segment depression	
Sensitivity	79%
Specificity	89%
(B) ST segment depression + elevation	
Sensitivity	87%
Specificity	89%
Coronary arteriography	
Coronary disease	= 154 patients
Single vessel	= 29
Two vessel	= 44
Three vessel	= 57
Left main stem	= 24
Normal coronaries	= 46 patients

Table 2 *Number of times ST segment depression was recorded in each precordial lead immediately after exercise in 200 patients*

Row	*A*	*B*	*C*	*D*
1	2	12	43	21
2	3	48	89	49
3	2	55	95	45
4	7	41	57	35

after exercise was often recorded in leads other than those usually occupied by the standard chest leads (that is ST segment elevation recorded in the standard precordial leads represented only 42% of the total projection to the 16 precordial leads).

False positive exercise-induced ST segment depression was recorded in almost all of the 16 precordial leads and was not confined or more frequent in any particular set of leads (Table 4). ST segment elevation in patients without prior myocardial infarction was confined to the right chest leads and was found in eight patients; six of these patients had ST segment depression also (Table 5). All patients with exercise-induced ST segment elevation had coronary disease at coronary angiography.

PATTERN OF PROJECTION OF ST SEGMENT CHANGES

In all 20 patients in whom recordings were made during exercise ST segment depression was first recorded in a small number of leads and increased in area as exercise continued. After the end of exercise, after an initial further increase in the number of leads with ST segment depression in eight (40%) patients, the area decreased. The first lead with ST segment depression was invariably the lead with the most severe ST segment depression at peak exercise and the same lead was the last to return to normal. An example is shown in Fig. 2.

Table 3 *Number of times ST segment elevation was recorded in each precordial lead immediately after exercise in 200 patients*

Row	*A*	*B*	*C*	*D*
1	18	17	11	1
2	22	20	13	1
3	11	15	8	1
4	3	7	5	0

Table 4 *Number of times false positive ST segment depression was recorded in each precordial lead immediately after exercise in four patients*

Row	*A*	*B*	*C*	*D*
1	0	1	0	0
2	0	1	2	2
3	0	3	3	1
4	1	3	3	1

Table 5 *Number of times ST segment elevation was recorded in each precordial lead immediately after exercise in eight patients without previous myocardial infarction*

Row	*A*	*B*	*C*	*D*
1	8	4	0	0
2	8	3	0	0
3	4	0	0	0
4	1	0	0	0

Table 6 *Number of times ST segment changes were confined to individual vertical or horizontal rows*

Row	*ST segment depression*	*ST segment elevation with past myocardial infarction*	*ST segment elevation without past myocardial infarction*
A	0	0	2
B	6	1	0
C	20	0	0
D	1	0	0
1	3	0	1
2	1	0	0
3	2	2	0
4	4	0	0

Analysis of the ST segment projection immediately after the end of exercise in 200 patients showed that on only five occasions was the ST segment alteration confined to one lead (those were C2, C3, C4, B3, B4). The number of times ST segment alterations were confined to one of the horizontal or vertical rows is shown in Table 6. Though ST segment changes in vertical row A occurred 29 times, on no occasion was ST segment depression confined to this row. In two patients ST segment elevation was seen only in row A.

Discussion

In 1932, Wolferth and Wood[9] described the first chest lead that proved of value in clinical medicine and their work stimulated clinical interest in precordial leads. They obtained a recording which they called the fourth lead (lead IV) by placing the left arm electrode over the apex of the heart and connecting the galvanometer to the lead III circuit. After this many other new leads were introduced including those based on the concept of the "exploring" electrode and "indifferent" electrode, as described by Wilson and his associates.[10] Many different areas were suggested for the exploring electrode, but the majority were over the anterior surface of the chest, particularly over the area of the heart. By convention the exploring electrode was arbitrarily placed in the standard six positions now used, connected through a central terminal.[10] Thus, there followed the CT 1-6 series of leads which, for convenience, were labelled V1-6 as presently used. In almost 50 years which have followed there has been no study investigating the relative merits of these standard lead positions in identifying ST segment abnormalities.

In recent years there has been a surge of interest in non-invasive diagnosis in cardiology, and, in particular, exercise testing and ambulatory monitoring are being used with increasing frequency.[11 12] If we are to make optimal use of these techniques, however, it is necessary to know much more about the projection of

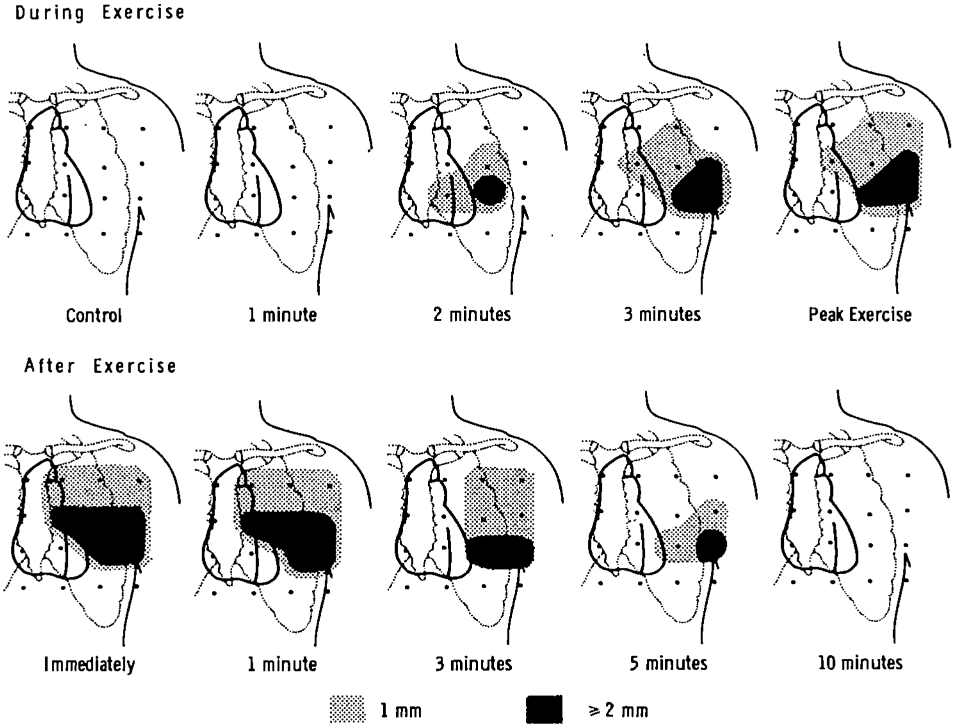

Fig. 2 *A sequence of contour maps has been drawn of the projection of ST segment depression on to the front of the chest in a single patient. The first leads in which ST segment depression was recorded were those with the most severe ST segment depression at peak exercise and the last to return to normal after exercise.*

ST segment abnormalities on to the front of the chest. Whether only a single lead or multiple leads are used for the exercise test, it is necessary to have some concept of the pattern and distribution of ST segment changes in patients with ischaemic heart disease; the same holds true particularly in ambulatory monitoring where there are only two exploring electrodes available.

We have studied the projection of ST segment changes during and after a maximal exercise test using 16 precordial leads arranged over the left hemithorax in a matrix. The ST segment projects on to the front of the chest during exercise in a uniform manner. The area (that is number of leads involved) increases as exercise progresses and then shrinks after exercise in a reciprocal fashion. In a substantial number of patients the area continues to increase for up to three minutes after exercise before decreasing. The lead that first shows the ST segment depression is almost invariably the lead in which the most severe ST segment depression is found and the last in which it disappears. This suggests that ischaemia starts in one site, increases in area as the provocation continues, and then afterwards gradually recedes. The use of multiple leads arranged in a matrix will therefore have advantages in determining the effects of interventions over the conventional, arbitrarily placed chest leads.

This study has shown that ST segment depression in an exercise test will project over the front of the chest in a pattern that is individual to each patient. The projection will be related to the site, severity, and extent of ischaemia in each patient and be modified by a number of non-cardiac factors, that is chest size and shape, resistance of tissue between the heart and chest wall, etc. Projection of ST segment depression involving the standard leads of the electrocardiogram was seen to represent only 41% of the total projection; and ST segment elevation to represent 42%. In 31% maximal ST segment alteration was projected outside the area subtended by the standard leads and in 19% there were no ST segment alterations in the two standard positions usually selected for 24 hour monitoring.

Ambulatory monitoring of ST segments is performed using recorders that have two exploring electrodes; usually these are placed in an anterior (V5) and inferior site. Failure to record ST segment changes in patients complaining of chest pain may thus mean that the wrong site has been selected for placing the exploring electrode. Previous studies have shown that to obtain the maximal information from ST segment ambulatory monitoring it is necessary to record not only from a site where ST segment depression is known to occur but where it occurs maximally. Moving one or both of the exploring electrodes to a more superior position of our 16 lead matrix in subsequent recordings may then provide diagnostic information that otherwise would have been missed.

Almost all electrocardiograph machines used for exercise testing have three recording channels. In this study we have analysed the precordial projection to determine if a matrix arrangement can be maintained in such a way that the recording could be performed with a three channel electrocardiogram machine without loss of important data. Row A was involved in 35% of the total projection of ST segment elevation and 2% of the total projection of ST segment depression. In only two patients were the ST segment alterations confined to this row and in none was ST segment depression seen only in this row. We, therefore, recommend that a precordial mapping system could be satisfactorily obtained using 12 precordial leads (rows B, C, and D). Recording of the limb leads should also be performed since, though inferior changes are usually projected to the bottom row of the map, recording the inferior limb leads would ensure no information is lost.

In 1967 Mason and his colleagues[11] introduced the standard 12 leads into exercise testing. We now recommend that an 18 lead system using 12 precordial leads arranged as a matrix has important advantages, particularly as it allows the precordial projection of ST segment changes to be evaluated in each individual patient. This may be undertaken without requiring any new equipment other than a switching box and a little extra effort in placing the electrodes.

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Precordial ST segment depression in patients with inferior myocardial infarction: clinical implications

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SUMMARY A prospective assessment of precordial ST segment depression in acute inferior myocardial infarction was made comparing clinical characteristics, and the hospital and post-hospital course. One hundred and ten consecutive patients with inferior infarction and without previous infarction were allocated to three electrocardiographic groups. Group 1 consisted of 35 patients with inferior or inferolateral infarction without precordial ST depression. Group 2 consisted of 59 patients with 1 mm or more precordial ST depression, subdivided into 36 patients with transient ST depression (2t) and 23 patients with ST depression persisting for 48 hours or more after the admission electrocardiogram (2p). Group 3 had 16 patients with definite inferoposterior or inferoposterolateral infarction. Patients in group 2 were older than those in group 1, had higher peak creatine kinase levels, and had atrial fibrillation and atrioventricular block requiring treatment more frequently. These clinical differences were largely contributed by subgroup 2p. Compared with group 1, subgroup 2p contained relatively more women and there were more instances of ventricular fibrillation and left ventricular failure. The hospital stay was longer in this subgroup. Compared with group 3, patients in group 2p were older, had a greater proportion of women, and were more commonly previously hypertensive. Patients in subgroup 2t had higher creatine kinase levels and more frequent atrioventricular block than those in group 1. Differences in hospital mortality and in other clinical features were not significant among the groups. During a mean follow-up period of 17 (12 to 32) months left ventricular failure was more common in subgroup 2p compared with groups 1 and 2t and recurrent infarction occurred more often in subgroup 2p compared with group 1. No late deaths occurred in groups 1 and 3, but three (5%) patients in group 2 died.

Our data show that persistent precordial ST depression in patients with inferior infarction is a reliable marker of an adverse hospital and post-hospital course.

The extent of myocardial damage and the presence of multivessel coronary artery disease are major prognostic factors in acute myocardial infarction.[1–3] Precordial ST segment depression with inferior myocardial infarction may indicate ischaemia or infarction of the anteroseptal region, posterior left ventricular wall, or both. Alternatively, these changes may be "reciprocal" to ST changes in the inferior electrocardiographic leads. Hence, identification of the significance of precordial ST segment depression in inferior infarction may have important clinical implications.

Precordial ST changes in inferior infarction have been assessed in terms of myocardial involvement by nuclear scanning techniques[4–7] and coronary arteriographic findings.[5 8 9] The conflicting results reported may reflect differences in patient selection or in the electrocardiographic diagnosis and interpretation of precordial ST segment depression. In particular, the significance of persistent ST depression has not been previously examined in detail. Persistent ST depression, despite resolution of inferior ST elevation, may indicate significant ischaemia or even infarction rather than a reciprocal phenomenon.

In this study of patients with inferior infarction, the implications of precordial ST depression are evaluated by comparison of clinical characteristics, and hospital and post-hospital morbidity and mortality.

Patients and methods

The study comprised 110 consecutive patients with

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acute transmural inferior infarction, without previous infarction, admitted to Prince Henry's Hospital Coronary Care Unit, Melbourne, between April 1978 and January 1980.

A diagnosis of acute inferior transmural infarction was based on: (i) a history of prolonged chest pain suggesting myocardial ischaemia, occurring within 48 hours before admission; (ii) development of pathological Q waves (>1 mm deep, $\geq$0·04 s in duration) in electrocardiographic leads II, III, and aVF, and (iii) characteristic serial changes in serum levels of creatine kinase and lactic dehydrogenase.

Patients with previous myocardial infarction or left bundle-branch block were excluded.

ELECTROCARDIOGRAPHIC CLASSIFICATION

All patients showed changes of transmural infarction (development of abnormal Q wave, ST segment elevation, and T wave inversion) in leads II, III, and aVF.

A diagnosis of inferolateral infarction was made when these abnormalities also appeared in leads V5 and V6. Associated posterior infarction was diagnosed when the electrocardiogram showed the development of prominent primary R waves in leads V1 and V2 (R/S $\geq$1) with related ST depression and tall, wide, symmetrical T waves in leads V1 and V2.

The electrocardiograms of patients with inferior and inferolateral infarction were subclassified according to the presence or absence of significant ST segment depression ($\geq$1 mm deep, $\geq$0·08 s) in at least two of the chest leads V1 to V4. Thirty-five patients had inferior or inferolateral infarction without significant precordial ST depression (group 1). Fifty-nine patients had inferior or inferolateral infarction with associated precordial ST depression (group 2). The ST depression resolved within 48 hours of admission in 36 of these 59 patients—subgroup 2t ("transient" ST depression). Also included in this subgroup were those patients whose electrocardiogram showed precordial ST depression, but who died within the first 48 hours. Of the 59 patients, 23 had ST depression which persisted for at least 48 hours—subgroup 2p ("persistent" ST depression).

Group 3 comprised 16 patients with definite electrocardiographic evidence of posterior infarction.

FOLLOW-UP

The follow-up period ranged from 12 to 32 months (mean 17 months). At the time of follow-up three patients (3%), two from group 1 and one from group 3, could not be reached by letter, telephone, or through the local medical officer or the government statistician.

STATISTICAL ANALYSIS

Data are expressed as mean ± SEM. Assessment of the statistical significance of differences between two electrocardiographic groups was based on the unpaired t test and Fisher's exact test as appropriate. A p value of <0·05 was considered significant.

Results

PATIENT CHARACTERISTICS (Table 1)

Patients with persistent precordial ST depression (2p) had a mean age of 62 years, which was significantly older than those in all other groups ($p < 0·05$).

Men predominated in all groups, except subgroup 2p which had an almost equal sex ratio ($p<0·05$).

Angina before infarction occurred with similar frequency in groups 1 and 2. In group 3, eight (50%) patients had previous angina (NS).

Of subgroup 2p, 52% had been hypertensive before hospital admission, compared with subgroup 2t ($p<0·05$) and group 3 ($p<0·05$). Comparison with group 1 did not reach statistical significance.

The time from onset of symptoms to the initial electrocardiogram was similar in patient groups.

HOSPITAL COURSE (Table 2)

The average hospital stay for subgroup 2p was 14 days compared with 10 days for group 1 ($p<0·05$). Groups 2 and 3 had similar periods in hospital.

The mean peak creatine kinase level of group 2 patients was 1779 U/l which was significantly higher ($p<0·001$) than that of those in group 1 (1090 U/l). The levels in subgroups 2t and 2p and group 3 were comparable and were all higher ($p<0·005$) than in group 1.

Sinus and junctional bradycardia and paroxysmal supraventricular tachycardia occurred with similar frequency in each of the groups. Only one patient (3%) in group 1 developed atrial fibrillation compared with 10 (17%) from group 2 ($p<0·05$). Of these 10 patients in group 2, seven were in subgroup 2p and three were in subgroup 2t ($p<0·05$). Two patients in group 3 had atrial fibrillation. Atrial flutter occurred in one patient (4%) from group 2p.

Although ventricular arrhythmias (including ventricular fibrillation) appeared to be more common in group 2 than in group 1, this difference was not statistically significant. Ventricular fibrillation, however, was significantly more common in subgroup 2 than in group 1 (22% vs. 3%, $p<0·05$). Ventricular arrhythmias, including fibrillation, occurred with comparable frequency in groups 1 and 3.

Atrioventricular block, requiring intravenous atropine or temporary pacing, occurred in 18 patients (31%) in group 2 but in only one (3%) patient from group 1 ($p<0·001$). Patients in subgroups 2t and 2p had a similar incidence of atrioventricular block (28% and 35%, respectively). Two (13%) group 3

Table 1 *Clinical characteristics*

	Group 1	*Group 2*			*Group 3*
		Total 2	*2t*	*2p*	
Number of patients	35	59	36	23	16
Age (y)	54±2	59±1*	56±2	62±2‡	54±3
Male:female	5:1	2:1	4:1	1:1†	7:1
Past angina	8 (23%)	15 (25%)	8 (22%)	7 (30%)	8 (50%)
Past hypertension	10 (29%)	21 (36%)	9 (25%)	12 (52%)	3 (19%)
Time from onset of symptoms to initial electrocardiogram (h)	8±2	5±1	5±1	5±2	3±1

*p < 0·05.
†p < 0·01.
‡p < 0·005.
p value in Tables 1–3 refers to the difference between group 1 and group indicated.

Table 2 *Hospital course*

	Group 1	*Group 2*			*Group 3*
		Total 2	*2t*	*2p*	
Hospital stay (d)	10±1	13±1	12±1	14±2*	12±1
Peak creatine kinase (normal <220 U/l)	1090 ±112	1779‡ ±112	1798‡ ±149	1774‡ ±161	1794‡ ±238
Atrial fibrillation	1 (3%)	10 (17%)*	3 (8%)	7 (30%)‡	2 (13%)
Ventricular arrhythmias needing treatment	19 (54%)	40 (68%)	26 (72%)	14 (61%)	8 (50%)
Ventricular fibrillation	1 (3%)	9 (15%)	4 (11%)	5 (22%)*	1 (6%)
Atrioventricular block needing treatment	1 (3%)	18 (31%)**	10 (28%)‡	8 (35%)‡	2 (13%)
Left ventricular failure					
Mild	8	19	8	11*	3
Moderate	1	6	1	5*	3
Severe	1	2	2	—	1
Total	10 (29%)	27 (46%)	11 (31%)	16 (70%)‡	7 (44%)
Further infarction	2 (6%)	—	—	—	—
Death	1 (3%)	5 (8%)	2 (6%)	3 (13%)	2 (13%)

*p<0·005.
‡p<0·005.
**p<0·001.

Table 3 *Follow-up data*

	Group 1	*Group 2*			*Group 3*
		Total 2	*2t*	*2p*	
Hospital survivors	34	54	34	20	14
Angina pectoris	12 (35%)	19 (35%)	16 (48%)	3 (15%)	4 (29%)
Coronary graft surgery for severe angina	2	2	1	1	1
Supraventricular arrhythmias	—	4	3	1	—
Ventricular arrhythmias needing treatment	1	3	2	1	—
Left ventricular failure	2 (6%)	14 (26%)*	5 (15%)	9 (45%)‡	3 (21%)
Recurrent infarction					
Anterior	—	4	2	2	—
Lateral	1	2	1	1	—
Uncertain site	—	2	1	1	—
Total	1(3%)	8 (15%)	4 (12%)	4 (20%)*	—
Death	—	3 (6%)	1 (3%)	2 (10%)	—

*p<0·05.
‡p<0·005.

patients had atrioventricular block needing treatment (NS).

Left ventricular failure was graded as mild, moderate, or severe.

Mild left ventricular failure was diagnosed in the presence of basal pulmonary crepitations not cleared with coughing, a third heart sound, and radiological pulmonary venous congestion. Moderate left ventricular failure was defined by the presence of the above signs, radiological interstitial or alveolar oedema, and a normal blood pressure. A diagnosis of severe left ventricular failure was made when the features just described were accompanied by arterial hypotension requiring inotropic support.

Cardiac failure developed in 10 (29%) group 1 and 27 (46%) group 2 patients (NS). Of the latter 27 patients, 16 (59%) were in subgroup 2p. The occurrence of left ventricular failure in 70% of this subgroup was more than twice that in group 1 ($p<0{\cdot}005$) and in subgroup 2t ($p<0{\cdot}005$). Seven patients (44%) in group 3 had left ventricular failure (NS).

Hospital deaths

One (3%) group 1 patient, a 69 year old woman with inferolateral infarction who developed cardiogenic shock, died within 24 hours of admission.

Five (8%) group 2 patients died who were older than 60 years, and three of whom were women. Two had cardiogenic shock, one had left ventricular rupture, one had severe mitral regurgitation and ventricular arrhythmias with cardiac failure, and one had intractable ventricular fibrillation.

Both (13%) group 3 patients who died were older than 70 years and were men. One developed cardiogenic shock and the other bronchopneumonia, on a background of ventricular arrhythmias, mitral regurgitation, and probable right ventricular infarction.

FOLLOW-UP DATA (Table 3)

Angina pectoris after discharge from hospital occurred with similar frequency in groups 1, 2, and 3. Of patients from subgroup 2t, 48% developed angina compared with 17% from subgroup 2p ($p<0{\cdot}05$). Of the 31 group 1 and 2 patients who developed angina, 12 (39%) had angina before the infarction. All four group 3 patients with post-infarction angina had pre-existent angina.

Coronary anatomy

Disabling angina was investigated by coronary arteriography in seven patients (two from group 1, four from group 2, and one from group 3). All seven had significant narrowing ($\geqslant$75% luminal diameter reduction) in a dominant right coronary artery. Disease was confined to this artery in two patients (both subgroup 2t) and operation was not recommended. Two patients (one from group 1, the other from group 3) had additional disease in the left anterior descending and left circumflex arteries, respectively. Triple vessel disease was found in the remaining three patients (one from group 1 and two from subgroup 2p). These five patients (two with double and three with triple vessel disease) were considered suitable for surgery and underwent aortocoronary bypass three to 31 months (mean 20 months) after the inferior infarction.

Three patients who died during the initial hospital admission had triple vessel disease, demonstrated at necropsy in two cases and by coronary arteriography performed because of severe acute mitral regurgitation and cardiac failure in the remaining one.

No correlation was found between the pattern of coronary disease and electrocardiographic criteria in this small select group.

Arrhythmias occurring after leaving hospital and which required treatment were documented in one (3%) group 1 patient and seven (44%) group 3 patients (NS).

Follow-up electrocardiograms

Features of previous inferior infarction were present in all electrocardiograms, except two which had returned to normal. There was electrocardiographic evidence of further infarction in seven patients. Among subgroup 2p patients, precordial ST depression had resolved in all but one patient.

As frequent electrocardiograms were not recorded routinely during the follow-up period, the exact time of resolution of the ST segment depression is not known.

Cardiac failure developed in two patients (6%) from group 1 and 14 (26%) patients from group 2 ($p<0{\cdot}05$). Groups 2 and 3 had a similar incidence of cardiac failure. Nine (39%) patients in subgroup 2p were found to have cardiac failure. This incidence was significantly higher ($p=0{\cdot}02$) than that for groups 1 and 2t. Comparison with the incidence of 23% in group 3 patients was not significantly different.

Myocardial infarction occurred in one (3%) group 1 patient and eight (14%) group 2 patients (NS). Of the eight group 2 patients, four were from subgroup 2p. Recurrent infarction developed in 20% of subgroup 2p compared with 3% of group 1 ($p<0{\cdot}05$).

There were no *deaths* at the time of follow-up among the 32 (94%) group 1 hospital survivors. Two patients were lost to follow-up. There were three deaths (6%) among group 2 hospital survivors. Two were associated with further myocardial infarction and one with respiratory failure caused by emphysema. All group 3 hospital survivors were alive at follow-up. One patient could not be traced.

Discussion

The modern trends in management of acute myocardial infarction include early identification of patients at high risk of subsequent coronary events. A more aggressive therapeutic approach aiming to preserve myocardial function and improve long term prognosis may be offered to such patients. This approach, however, poses serious logistic problems in many busy cardiology departments. Our findings suggest that patients at high risk after acute inferior infarction can be identified by simple electrocardiographic criteria.

Precordial ST segment depression in our patients with inferior infarction was associated with older age, higher creatine kinase levels, more frequent atrial fibrillation, significant atrioventricular block, and post-hospital cardiac failure. Other studies have shown higher creatine kinase levels and depressed ejection fraction in patients with acute inferior infarction and precordial ST depression.[4 5 7] Croft and colleagues[6] did not evaluate clinical variables, but found no difference in ejection fraction. We have been unable to find any previous publications on long term clinical evaluation of these electrocardiographic changes.

The time delay between onset of symptoms and the admission electrocardiogram was similar for groups 1 and 2. Therefore, precordial ST depression and its clinical implications could not be explained by differences in the times of electrocardiographic recording.

Analysis of the persistence of precordial ST depression has clearly defined an important clinical subset. Those patients in whom precordial ST depression was present for at least 48 hours after admission to hospital contributed much of the morbidity and mortality of group 2.

Infarct size, as assessed by peak creatine kinase levels, was similar in subgroups 2t and 2p. Left ventricular failure (acute and chronic) and atrial fibrillation, however, were more common in the latter subgroup. There are two possible explanations. First, patients with persistent precordial ST depression had a significantly higher incidence of past hypertension which may have led to some degree of impairment of underlying myocardial performance. Myocardial infarction in this setting may result in a greater tendency to left ventricular failure and atrial fibrillation. Secondly, persistent precordial ST depression may represent significant myocardial ischaemia either adjoining or remote from the region of inferior infarction. This could contribute to ventricular dysfunction and atrial fibrillation without necessarily affecting creatine kinase release.

Although persistent ST depression was associated with an adverse clinical course, even transient precordial ST depression correlated with higher peak creatine kinase levels and more frequent occurrence of atrioventricular block requiring treatment. Therefore, transient ST depression should not be dismissed as merely a "reciprocal" event.

There was a low occurrence of post-infarction angina in subgroup 2p compared with subgroup 2t. This observation is difficult to explain. The significantly higher incidence of symptomatic left ventricular failure in subgroup 2p, however, may have resulted in reduced exercise capacity manifest as dyspnoea rather than chest pain.

Although the groups were small, the patient numbers were sufficient to show statistically significant differences between groups 1 and 2. A larger number of patients in group 3 may have disclosed other significant differences among the groups.

Exercise stress testing, nuclear scanning, and coronary arteriography were not routinely performed since the study was designed to assess the clinical rather than the anatomical significance of precordial ST depression. It is of interest, however, that anterior transmural infarction developed in four (7%) group 2 patients but in none from groups 1 or 3. Furthermore, though comparison of subgroup 2p and group 3 ("true" posterior infarction) did show similar creatine kinase levels, there were major differences in patient characteristics.

Whatever the anatomical correlations of precordial ST segment depression in inferior infarction, the study has clearly shown a reliable marker of an adverse hospital and late clinical course.

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Complete transposition of great arteries with coarctation of aorta

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SUMMARY Complete transposition of the great arteries with ventricular septal defect and coarctation or atresia of the aortic arch is a relatively rare anatomoclinical entity and in general not well understood. This association accounted for six out of 50 cases (12%) of our clinical experience and six out of 64 cases (9%) of the post-mortem series of complete transposition. Relevant clinical manifestations were cyanosis, early and pronounced congestive heart failure, with a decrease in amplitude of femoral pulses and, in the most severe cases, isolated left ventricular hypertrophy on the electrocardiogram. Inlet or outlet right ventricular obstruction and pulmonary artery dextroposition are the pathological substrates of unequal partitioning of the blood stream in favour of the pulmonary artery and ductus arteriosus, probably accounting for fetal underdevelopment of the aortic arch. The medical and surgical prognosis of these cases is definitely poor.

Obstructive lesions of the aortic arch are usually associated with concordant atrioventricular and ventriculoarterial connection. They may, however, also be present in complete transposition of the great arteries (discordant ventriculoarterial connection with atrioventricular concordance), but they have only sporadically been described in the published reports.[1-5]

It is the purpose of this paper to report our experience with patients affected by complete transposition of the great arteries and coarctation of the aorta. The clinicopathological features of these cases are sufficiently distinctive to indicate that this complex of malformations is a real and not so rare anatomoclinical entity.

Subjects

Among 50 consecutive cases of complete transposition of the great arteries seen at the Pediatric Department of the University of Padua, between June 1975 and June 1980, six (12%) were found to have obstructive lesions of the aortic arch. There were five male and one female patient (Table 1), varying in age from 1 to 55 days (mean 18 days). In three the diagnosis was made by cardiac catheterisation and angiocardiography, five died (cases 1 to 5, Table 1) and came to necropsy, one is still alive (case 6, Table 1). Reviewing our anatomical collection, another specimen (case 7, see Table 3) was found with this association. The incidence in our necropsy series was 9% (six out of 64 hearts with complete transposition of the great arteries). Only those cases were considered with the pulmonary artery arising mostly (>50%) from the left ventricle and with the aorta arising entirely from the right ventricle; accordingly cases with double outlet right ventricle were excluded.

CLINICAL FEATURES

The clinical data are summarised in Table 1. All six patients presented with signs of congestive heart failure and cyanosis; in three the brachial and femoral pulses were equal and normal in amplitude, while in the others the femoral pulses were either absent or very weak; differential cyanosis was never observed.

In the electrocardiogram two out of six showed isolated left ventricular hypertrophy (Fig. 1, case 2) and two had biventricular hypertrophy; in one there was right ventricular hypertrophy and in the sixth the electrocardiogram was normal, when first seen at 1 day of age.

The chest x-ray showed cardiothoracic ratio varying from 0·58 to 0·78 and increased pulmonary vascularity in all the patients. An M-mode echocardiogram was recorded in one instance (Fig. 2, case 3): the right ventricular dimension was reduced; there were two atrioventricular valves with continuity between the posterior one and the pulmonary artery; the anterior great artery (aorta) was decreased in diameter.

Three patients (cases 4 to 6) underwent cardiac catheterisation (Table 2). The oxygen saturation

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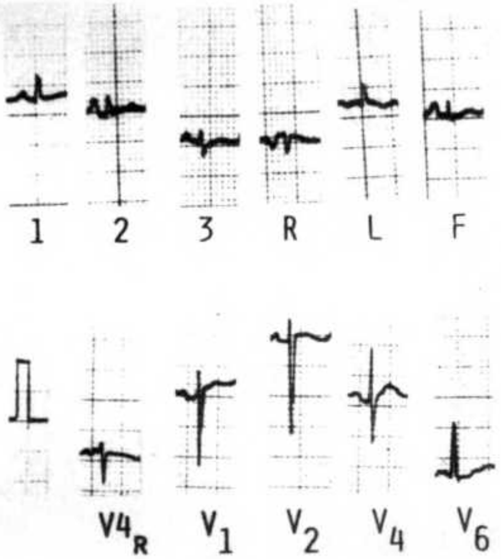

Fig. 1 *Case 2. Electrocardiogram, showing a QRS axis of +30°, left ventricular hypertrophy, and underdevelopment of the right ventricular electrical forces.*

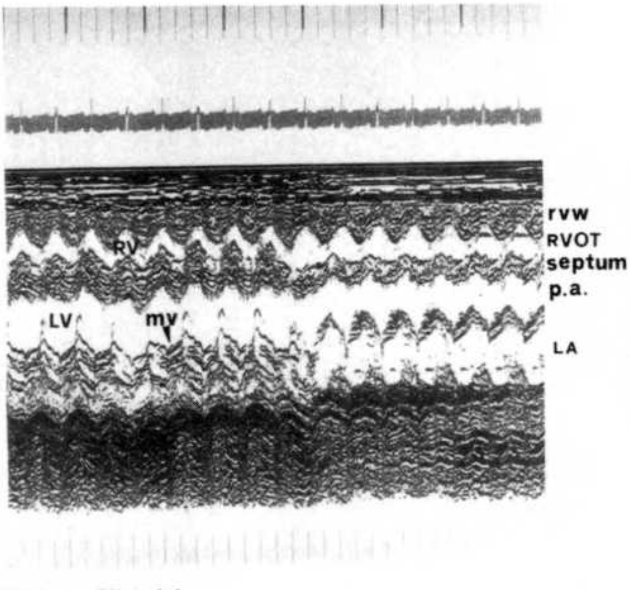

Fig. 2 *Case 3. M-mode echocardiogram showing decreased right ventricular dimension and mitropulmonary continuity. The anterior wall of the pulmonary artery is entirely aligned with the interventricular septum.*
Abbreviations: rvw, right ventricular wall; RVOT, right ventricular outflow tract; p.a., pulmonary artery; LA, left atrium; RV, right ventricle; LV, left ventricle; mv, mitral valve.

Table 1 *Clinical data*

Case No.	*Sex*	*Age on admission*	*Cyanosis*	*CHF*	*Femoral pulses*	*Electrocardiogram*		*X-ray*	
						LVH	*RVH*	*C/T*	*Pulmonary vascular markings*
1	M	1 d	1^+	3^+	Very weak	Yes	No	0·65	↑
2	M	6 d	1^+	3^+	Absent	Yes	No	0·78	↑ ↑
3	M	15 d	3^+	2^+	Normal	Yes	Yes	0·60	↑
4	M	55 d	1^+	2^+	Normal	No	Yes	0·60	↑
5	F	30 d	2^+	3^+	Normal	Yes	Yes	0·67	↑
6	M	1 d	2^+	1^+	Weak	No	No	0·58	↑
7*	M	5 mth	—	—	—	—	—	—	—

*Other clinical data not available.
Abbreviations: LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; C/T, cardiothoracic ratio; CHF, congestive heart failure.

Table 2 *Cardiac catheterisation data*

Pressure (mmHg)

Case No.	*RA M*	*RV S/D*	*Ascending aorta S/D M*	*Descending aorta S/D M*	*LA M*	*LV S/D*	*PA S/D M*	*After Rashkind procedure*	
								RA M	*LA M*
4	6	80/15	70/35 50		20	70/15	75/35 55	10	13
5	8	70/10	88/45 60	78/20 41	8	65/10	75/25 25		
6	3	80/4	80/40 60		5			0	0

showed a significant left-to-right shunt at the ventricular level in all of them. Pulmonary arterial hypertension was present in the two cases (cases 4 and 5) in which the pulmonary artery was entered; in only one case (case 5) was the descending aortic pressure obtained, showing a systolic gradient of 10 mmHg between ascending and descending aorta. In this case aortography showed a "stop" of the contrast medium at the aortic isthmus (Fig. 3a), which was interpreted as an atresia of the aortic arch, whereas the surgeon found a distinct coarctation. In all three patients a diagnosis of transposition of the great arteries with ventricular septal defect was made by right and left cineventriculography; in one (case 4) the coarctation of the aorta was not recognised clinically or at angiography.

In all the patients but one (case 6) the response to anticongestive treatment was poor. Cases 1 and 2 died three days and a few hours, respectively, after admission; case 3 died at 40 days of age with superimposed severe bilateral bronchopneumonia. Of the three catheterised patients, one (case 4) died of cerebral

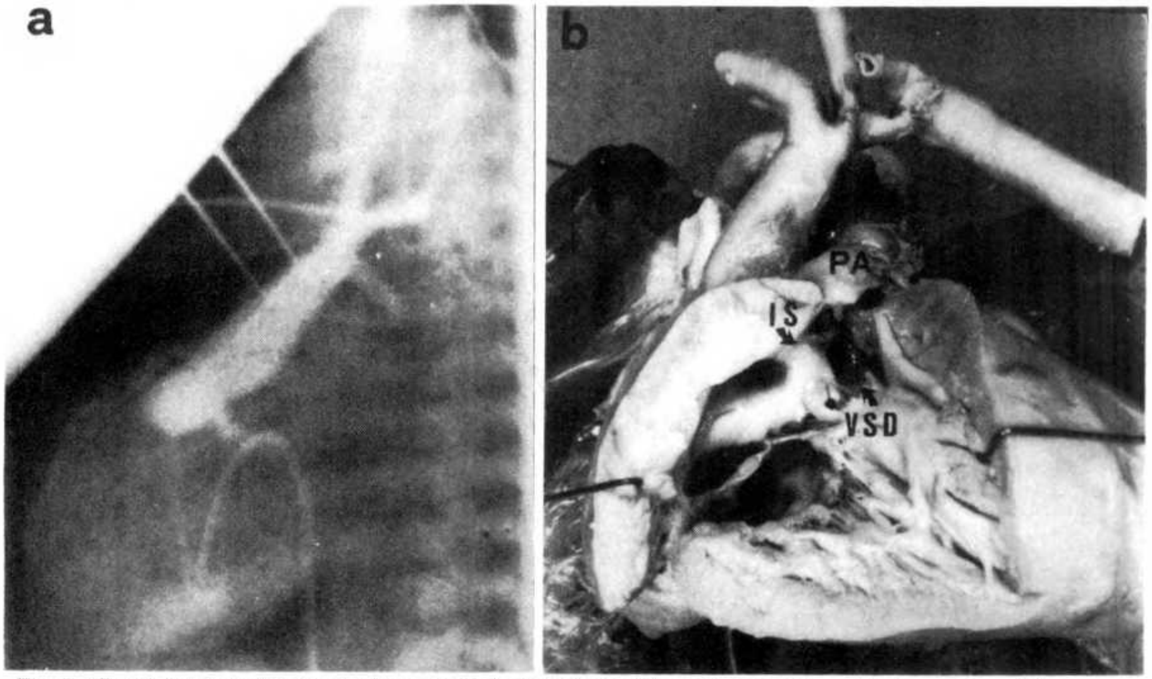

Fig. 3 *Case 5. (a) Ascending aortography shows tubular hypoplasia of the aortic arch with complete interruption of the contrast medium at the level of the aortic isthmus. (b) The right ventricular view of the heart specimen discloses a subaortic infundibular stenosis caused by rightward displacement of the infundibular septum (IS), moderate dextroposition of the pulmonary artery (PA), and the subpulmonary ventricular septal defect (VSD). Note the pulmonary banding and the surgically attempted relief of the aortic arch obstruction.*

O₂ Saturation (%)										
									After Rashkind procedure	
SVC	*RA*	*RV*	*Ascending aorta*	*Descending aorta*	*LA*	*LV*	*PA*	*PV*	*RV*	*Ascending aorta*
53	55	72	68		91					
70	75	84		94	98	95	90	96		
20	18	29	36		83	75		90	72	

Abbreviations: RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; PA, pulmonary artery; SVC, superior vena cava; M, mean pressure; S/D, systolic/diastolic pressure; PV, pulmonary vein.

haemorrhage five days after operation (persistent ductus arterious ligation plus pulmonary artery banding); another (case 5) died at 2 months of age, 48 hours after operation (resection of coarctation with end to end anastomosis of the aorta, pulmonary artery banding, and persistent ductus arteriosus ligation); the third (case 6) is the only patient who has survived and is now awaiting operation after a second cardiac catheterisation.

NECROPSY FINDINGS

The most relevant observations at necropsy are reported in Table 3. Visceroatrial situs solitus, laevocardia, atrioventricular concordance, and ventriculoarterial discordance were present in all the cases. The ascending aorta was small and the pulmonary artery large, the ratio between the diameters of the pulmonary artery and ascending aorta being more than 1·5:1 in three cases. Patent or closing ductus arteriosus

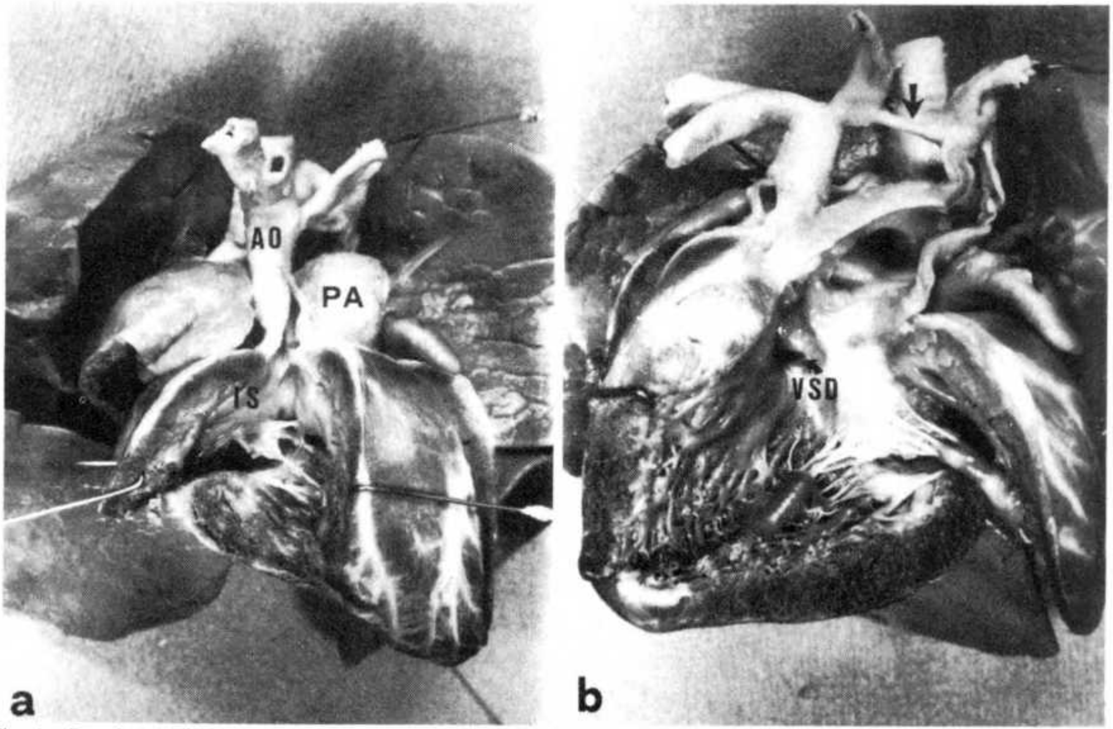

Fig. 4 *Case 2. (a) The right ventricle has a hypoplastic trabecular component and an obstructed aortic outflow resulting from anterior deviation of the infundibular septum (IS). Note the extreme dilatation of the pulmonary artery (PA) when compared with the small ascending aorta (AO). (b) The view from the left ventricle shows the ventricular septal defect (VSD) caused by infundibuloventricular malalignment and mild dextroposition of the pulmonary artery. Note the atretic aortic arch (arrow) between the left carotid and left subclavian artery.*

Table 3 *Necropsy findings*

Case No.	*PA/Ao diameter ratio*	*Right ventricle*			*VSD*	*% PA dextroposition*	*Aortic arch obstruction*	*PDA*
		Inflow	*Trabecular portion*	*Outflow*				
1	1·7:1	Normal	Moderate hypoplasia	Normal	Subpulmonary malalignment	40%	Atresia type A*	Large
2	2:1	Normal	Severe hypoplasia	Subaortic stenosis	Subpulmonary malalignment	10%	Atresia type B*	Large
3	1·2:1	Normal	Normal	Normal	Subpulmonary malalignment	20%	Preductal coarctation	Closing
4	1·3:1	Normal	Moderate hypoplasia	Subaortic stenosis	Subpulmonary malalignment	15%	Tubular hypoplasia	Closing†
5	1·5:1	Normal	Normal	Subaortic stenosis	Subpulmonary malalignment	30%	Preductal† coarctation	Closing†
6‡								
7	2:1	Very stenotic	Severe hypoplasia	Moderate hypoplasia	Perimembranous VSD	—	Atresia type A*	Closing

*Celoria and Patton classification.[6]
†Surgical observation.
‡Case 6 is still alive.
Abbreviations: PA, pulmonary artery; Ao, ascending aorta; VSD, ventricular septal defect; PDA, persistent ductus arteriosus.

was observed in four cases, while in two it had been surgically ligated. The aortic arch appeared atretic in three instances, type A of Celoria and Patton[6] in two and type B in one; preductal coarctation was present in two and tubular hypoplasia in one. All specimens had an associated ventricular septal defect. In five the defect was subpulmonary because of infundibuloventricular malalignment and the pulmonary artery was dextroposed, its origin from the right ventricle varying from 10 to 40% (Fig. 3b, 4). In three of these the infundibular septum showed an anterior displacement, creating subaortic narrowing. The right ventricle was underdeveloped in three hearts, mostly in its trabecular component.

In the sixth specimen, instead, the ventricular septal defect was small, perimembranous, and the pulmonary artery arose entirely from the left ventricle. The tricuspid valve appeared very stenotic and the right ventricle extremely hypoplastic (Fig. 5).

In all the cases mitro-pulmonary fibrous continuity was present.

Discussion

Complete transposition of the great arteries is usually classified into three physiological clinical entities: (1) simple transposition of the great arteries with intact ventricular septum characterised by conspicuous

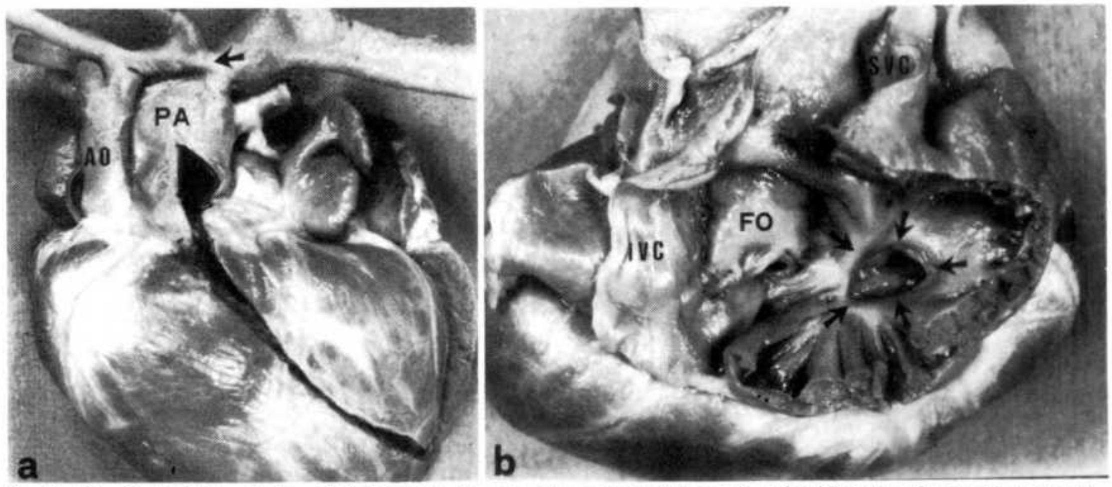

Fig. 5 *Case 6. (a) External view of the heart showing severe hypoplasia of the aortic arch with preductal coarctation (arrow), hypoplastic ascending aorta (AO), and dilated pulmonary artery (PA). (b) View of the opened right atrium showing that the tricuspid orifice is very small (arrows) compared with the fossa ovalis (FO). The foramen ovale is restrictive and the superior (SVC) and inferior (IVC) vena cavae are dilated.*

hypoxia, caused by lack of mixing between pulmonary and systemic circulation; (2) transposition of the great arteries with large ventricular septal defect in which signs of congestive heart failure predominate in the clinical picture; and (3) transposition of the great arteries with ventricular septal defect and pulmonary stenosis in which cyanosis is prominent, caused by decreased pulmonary blood flow, and the clinical findings parallel those in infants with tetralogy of Fallot.[7]

The syndrome of coarctation of the aorta in transposition of the great arteries has been considered extremely rare[8] and, accordingly, has never received sufficient attention. Our experience, together with other recent reports,[9 10] suggest that aortic arch anomalies are not so rare and the clinical manifestations and the pathological findings of this association are sufficiently distinctive as to be considered a separate nosographic entity among transposition of the great arteries.

Besides the presence of transposition of the great arteries and obstruction of the aortic arch, the following morphological features delineate this anatomical complex: (a) ventricular septal defect, always present, mostly subpulmonary and associated with dextroposition of the pulmonary artery; (b) mild to moderate right ventricular underdevelopment mainly of the trabecular component; and (c) right ventricular inflow, rarely, or outflow, more frequently, obstruction (caused by tricuspid stenosis or infundibular subaortic stenosis, respectively). Usually, the lower part of the systemic circulation is ductus-dependent.

From the clinical standpoint, cyanosis, early and severe congestive heart failure, and decreased amplitude of the femoral pulses characterise most of these patients. This picture of coarctation of the aorta in transposition of the great arteries is often associated with the presence of left ventricular hypertrophy on the electrocardiogram, either isolated (2/6) or combined with right ventricular hypertrophy (2/6). It is noteworthy that isolated left ventricular hypertrophy was observed just in those two cases with an atretic aortic arch and moderate to severe right ventricular hypoplasia. The decreased right ventricular electrical forces and the pressure and volume overload of the left ventricle account for this paradoxical electrocardiographic pattern in transposition of the great arteries.

Anterior displacement of the infundibular septum, as seen in three of our cases, has been suggested as a cause of subaortic stenosis in transposition of the great arteries, and obstruction of the aortic arch has also been described.[5 9 10] Unequal partitioning of the blood flow between the aorta and pulmonary artery in the presence of a ventricular septal defect may be advocated as the fetal pathogenetic mechanism for the underdevelopment of the aortic arch, as postulated for aortic arch anomalies in normally related great arteries.[11] Preferential blood streaming toward the pulmonary artery and ductus arteriosus may also be the result of inlet obstruction of the right ventricle, as in our case 7, or of dextroposition of the pulmonary artery, as in double outlet right ventricle with subpulmonary ventricular septal defect (Taussig-Bing), which is often associated with coarctation or interruption of the aorta.

In conclusion, we believe that, among transpositions of the great arteries, the form with aortic arch obstruction merits being viewed as a distinct physiological clinical type because it is relatively frequent and its pathological anatomy is distinctive.

This type of transposition is unfortunately associated with a worse clinical and surgical prognosis than is now the case in the other three major types.

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Accuracy and reliability of two indirect ambulatory blood pressure recorders: Remler M2000 and Cardiodyne Sphygmolog

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SUMMARY The Remler M2000 and Cardiodyne Sphygmolog are semiautomatic recorders designed to measure ambulatory blood pressure non-invasively. These recorders were assessed for accuracy and reliability in a study designed in three stages. Firstly, the interdevice variability was assessed separately for each type of recorder by comparing the recordings of three devices against each other and against simultaneous recordings by a mercury standard in 12 patients, multiple recordings being made in a random order in each patient. The mercury standard used was the London School of Hygiene (LSH) sphygmomanometer and the Hawksley random zero sphygmomanometer during assessment of the Remler and Sphygmolog, respectively. Though there were no differences between the three Remler recorders tested, one Sphygmolog recorder gave higher recordings than the two other Sphygmolog recorders tested because of a zero drift of 3 to 4 mmHg in the pressure transducer. Remler recordings were higher than simultaneous LSH sphygmomanometer recordings for both systolic and diastolic pressures. In the second part of the study, the Remler was compared with the Hawksley using simultaneous recordings in the same arm in 58 patients. No difference was found between Hawksley and Remler recordings. The discrepancy between this and the Remler-LSH comparison resulted from a tendency for the LSH sphygmomanometer to underestimate blood pressure. Similarly, the Sphygmolog recordings were compared with simultaneous Hawksley recordings in 100 patients. No significant difference was found between paired systolic pressure recordings though Sphygmolog recordings underestimated diastolic blood pressure. In the third part of the study, the reliability of the Remler was assessed from 69 attempted day recordings. Five Remler day recordings failed, a major cause of lost recordings being a defect in the microphone lead. The reliability of the Sphygmolog was compared with the Remler by attempting day recordings with each device in 13 patients. The reliability of the Sphygmolog was significantly poorer, only five of 13 Sphygmolog day recordings being decodable because of dislodgement of the recording disc during ambulation.

Single clinic recordings may not reflect the blood pressure behaviour of many patients.[1–3] Therefore, methods of assessing blood pressure behaviour outside the clinic have been developed and include home recording by the patient[4 5] or a relative,[6] and intra-arterial[1] and indirect ambulatory recording.[7 8]

Intra-arterial recording is an invasive procedure which is not without risk.[9] Home recording may be inaccurate because of patient bias.[10] Indirect ambulatory blood pressure recording should be free of these disadvantages but there have not been many studies on the accuracy of the recorders that are now available.

In this paper we present our findings on the accuracy and reliability of two ambulatory blood pressure recorders, the Remler M2000 and Cardiodyne Sphygmolog.

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Methods and results

The Remler M2000 is a portable blood pressure recorder consisting of a cuff and microphone connected to a pressure transducer and microcassette

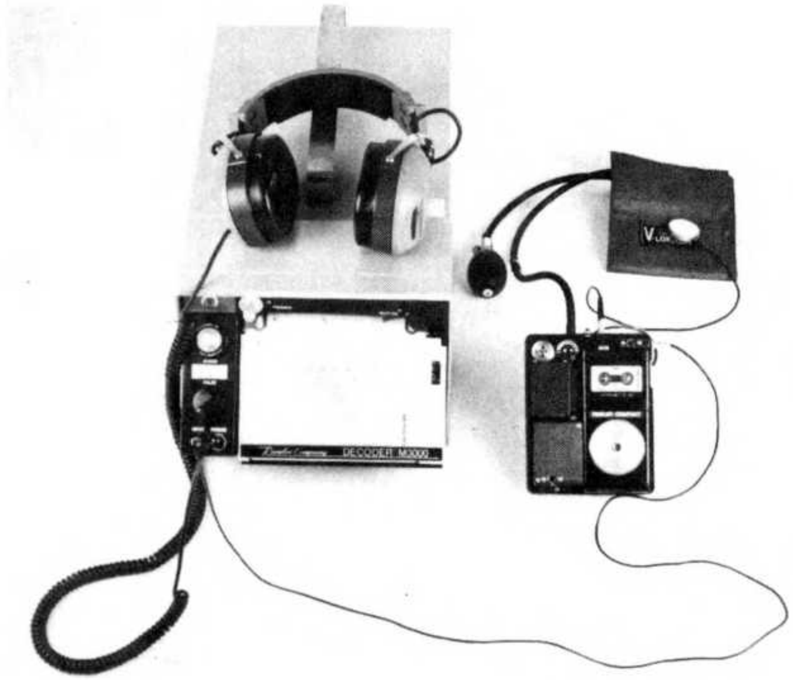

Fig. 1 *The Remler M2000 (right) and decoder (left) with example of pressure recording on the strip chart.*

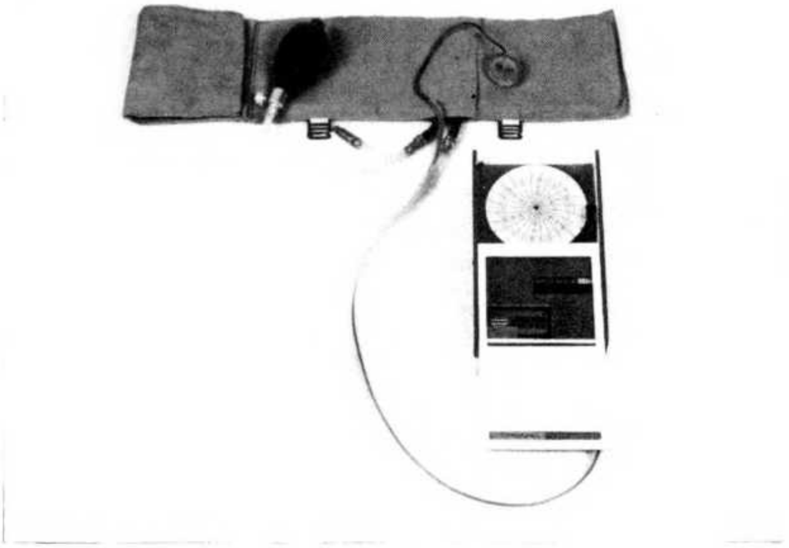

Fig. 2 *The Cardiodyne Sphygmolog.*

recorder worn on the patient's waist (Fig. 1). The cuff is inflated by the patient at prescribed intervals and deflates automatically. During deflation the Korotkoff sounds and cuff pressure are recorded on a magnetic tape. The tape is later analysed through a separate decoder which gives a strip chart recording of the sounds superimposed on a tracing of cuff pressure (Fig. 1). The pressures corresponding to the first and last sounds are recorded as the systolic and diastolic end-points, respectively. As weaker sounds may not deflect the pen in the decoder an observer listens to the tape during decoding and marks on the pressure tracing the position of the first and last sounds. Pen deflections caused by artefacts can be excluded at the same time.

The Cardiodyne Sphygmolog also consists of a sphygmomanometer cuff which is inflated by the patient and which deflates automatically through a needle valve (Fig. 2). The cuff pressure is monitored by a pressure transducer which drives a pen suspended over a paper disc. The Korotkoff sounds are detected by a microphone placed beneath the lower cuff margin and are recorded on to the paper disc by the pen as it moves across the disc. As the disc is calibrated for pressure, the first and last pen marks are recorded as the systolic and diastolic point, respectively. The paper disc is driven by a clockwork mechanism and revolves once in 24 hours. In this way, a real-time recording of daily blood pressures is made. Furthermore, the blood pressure recordings are read directly from the disc, so that a separate decoder or analyser is not required.

For each instrument three devices were tested to detect interdevice variability, a source of possible error in automated devices[11] which may bias the overall assessment of their accuracy. The accuracy of one of each type of recorder was then tested against a mercury standard. As the decision end-points for systolic and diastolic pressures are observer dependent, inter-observer variability in the decoding of pressure recordings was also assessed. The results were analysed by Student's t test for paired data and by linear regression analysis. In all cases phase V was used as the diastolic end-point.

ACCURACY STUDIES

(1) Interdevice variability

The Remler was compared with the London School of Hygiene (LSH) sphygmomanometer[12] in 12 patients as part of an interdevice variability study of three Remler recorders. Paired LSH sphygmomanometer and Remler recordings were made in the same arm by connecting both devices to a single cuff through a Y connector (Fig. 3a). The stethoscope head and microphone were applied to the same brachial artery without difficulty. Simultaneously a second observer recorded paired Remler-LSH sphygmomanometer recordings in the opposite arm by the same technique. As the two cuffs were interconnected we were able to compare simultaneous Remler recordings in opposite arms and also simultaneous Remler and LSH sphygmomanometer recordings in the same arm. The order of Remler recorders, the arm to which the recorders were applied, and the observers was randomised according to a Graeco-Latin square design. In this way observer and sequential bias, or bias resulting from differences between arms would not influence results. The rate of deflation of the system was set at 3 mmHg per second as we observed that lower deflation rates caused attenuation of the Korotkoff sounds.

The interdevice variability of the Cardiodyne Sphygmolog was assessed in the same way (Fig. 3a) except that instead of the LSH sphygmomanometer the Hawksley random-zero sphygmomanometer[13] was used as the mercury standard.

There was no significant difference between observers or between the three Remler recorders (Table 1). Remler recordings were higher than LSH sphygmomanometer recordings for both systolic and diastolic blood pressures, the mean differences being 4·8 mmHg ($p<0{\cdot}05$) and 4·7 mmHg ($p<0{\cdot}005$), respectively. This was true whether the mean Remler and LSH sphygmomanometer recordings for each of the 12 patients (Fig. 4) or individual recordings were compared. Furthermore, the mean differences between paired Remler and LSH sphygmomanometer recordings were negatively correlated with heart rate for diastolic ($r, -0{\cdot}69$ $n=12$, $p<0{\cdot}02$) but not systolic blood pressures.

Table 1 *Comparison of three Remler recorders*

	Systolic (mmHg)	*Diastolic (mmHg)*
Remler 1	161·6±4·5	94·7±1·8
Remler 2	163·4±4·4	93·7±2·1
Remler 3	161 ±4·3	93·4±1·6

Values are mean ± SEM.

Overall, there was no significant difference between paired Sphygmolog and Hawksley recordings in the 12 patients whether the mean data for each patient or individual recordings were compared. One Sphygmolog recorder (S_1), however, significantly overestimated paired Hawksley systolic recordings (Table 2) and comparison of individual paired Sphygmolog recordings in opposite arms showed that S_1 recordings were higher than S_2 and S_3 recordings, the mean difference being 4·3 mmHg ($p<0{\cdot}01$) for systolic and 2·4 mmHg ($p<0{\cdot}06$) for diastolic recordings. S_2 and S_3 Sphygmolog recordings tended to underestimate Hawksley diastolic pressure recordings (by 2·8 mmHg on average) while S_1 recordings showed a mean excess of 0·7 mmHg over the Hawksley.

Table 2 *Comparison of paired Hawksley and Sphygmolog recordings for three Sphygmolog recorders*

	Systolic (mmHg)			*Diastolic (mmHg)*		
	S_1	S_2	S_3	S_1	S_2	S_3
No.	48	48	48	48	48	48
Hawksley	162 ±5·5	161·6±5·3	162±5·4	90 ±1·9	91·3±1·7	91·1±2·0
Sphygmolog	165·6±5·8**	164·8±5·0	161±5·2	90·7±1·8	88·4±1·6*	88·4±1·7*

Values are mean ± SEM. *p<0·05, **p<0·01 significantly different from paired Hawksley recordings.

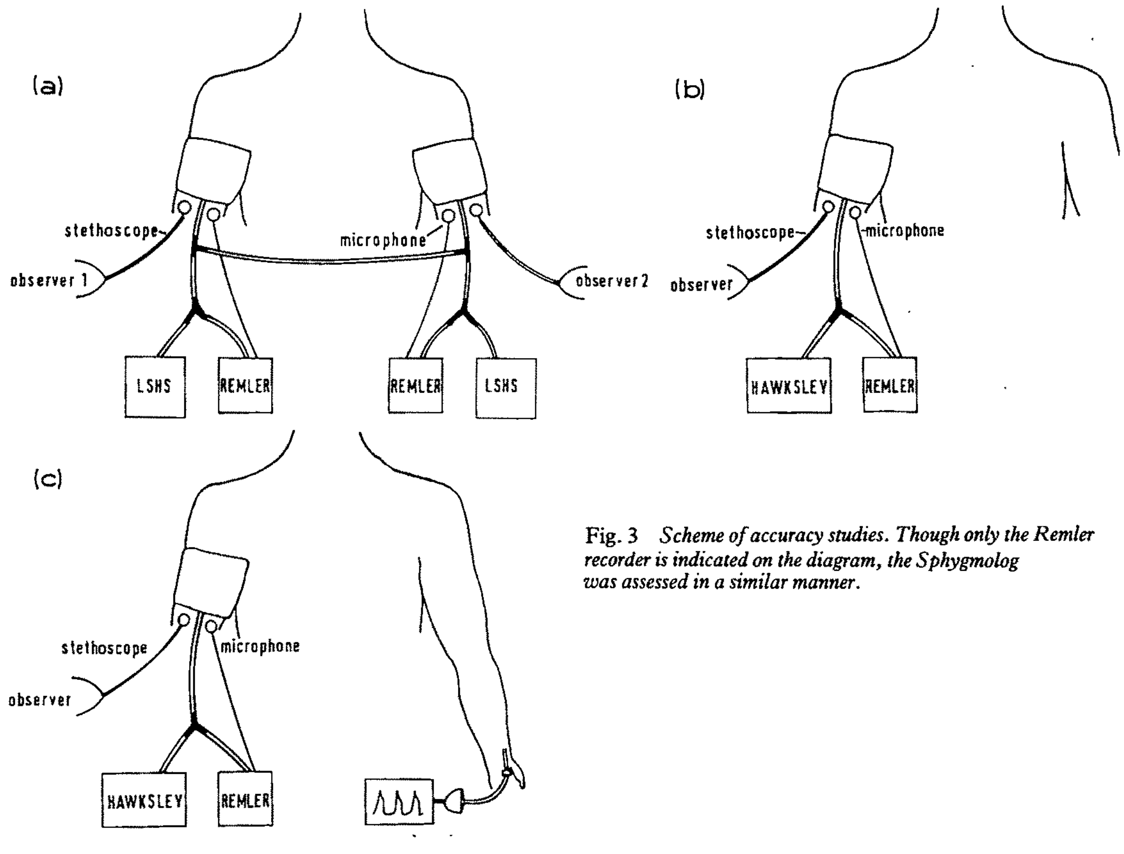

Fig. 3 *Scheme of accuracy studies. Though only the Remler recorder is indicated on the diagram, the Sphygmolog was assessed in a similar manner.*

(2) Comparison of simultaneous Hawksley and automatic device recordings

The Remler was compared with the Hawksley random zero sphygmomanometer in 35 patients using simultaneous recordings in the same arm (Fig. 3b). One Remler recorder and one observer were used. Two recordings were made in each patient as not all Remler recordings would be decodable. There was no significant difference between paired Remler and Hawksley recordings using either the mean data for each patient or individual recordings (Table 3).

Similarly, the Cardiodyne Sphygmolog was compared with the Hawksley random zero sphygmomanometer in 100 patients (Fig. 3b), one recording being made in each patient. There was no significant difference between paired systolic recordings (Table 3). Sphygmolog recordings, however, slightly underestimated Hawksley diastolic recordings, the mean difference being 2 mmHg.

(3) Comparison of Remler and intra-arterial recordings

In 23 patients, simultaneous Hawksley and Remler recordings were made in the left arm while intra-arterial recordings were recorded from the opposite

Table 3 *Comparison of paired Hawksley and Remler recordings and paired Hawksley and Sphygmolog recordings: Data for Hawksley-Remler recordings represent mean data (± SEM) for each of 35 patients*

	Systolic (mmHg)		*Diastolic (mmHg)*	
	Hawksley	*Remler*	*Hawksley*	*Remler*
No.	35	35	35	35
Mean ± SEM	162·2±5·0	161·8±5·1	99·5±2·8	99·9±2·8
Correlation coefficient	0·98		0·97	
	Hawksley	*Sphygmolog*	*Hawksley*	*Sphygmolog*
No.	100	100	100	100
Mean ± SEM	160·1±3·0	159·0±2·9	93·8±1·7	92±1·8*
Correlation coefficient	0·98		0·97	

*p<0·001, significantly different from paired Hawksley recordings.

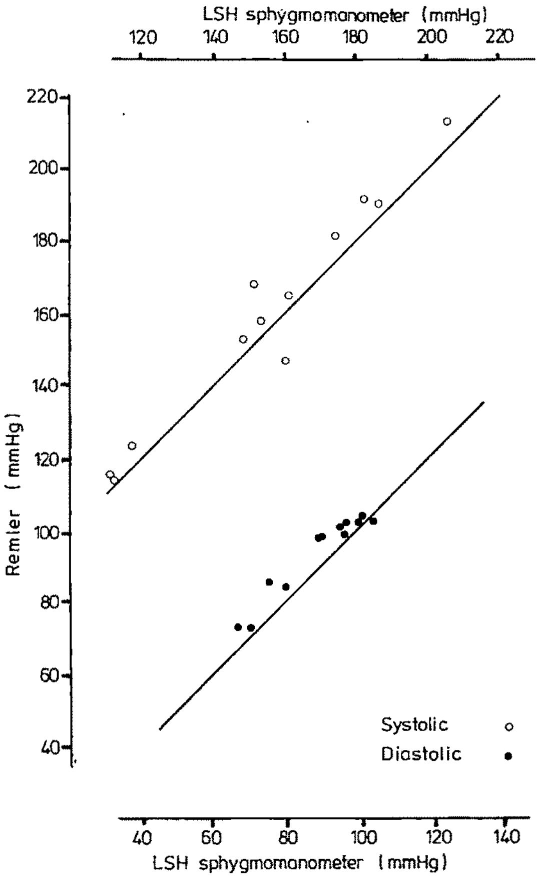

Fig. 4 *Comparison of mean LSH sphygmomanometer and Remler paired recordings in each of 12 patients. Lines of identity are given.*

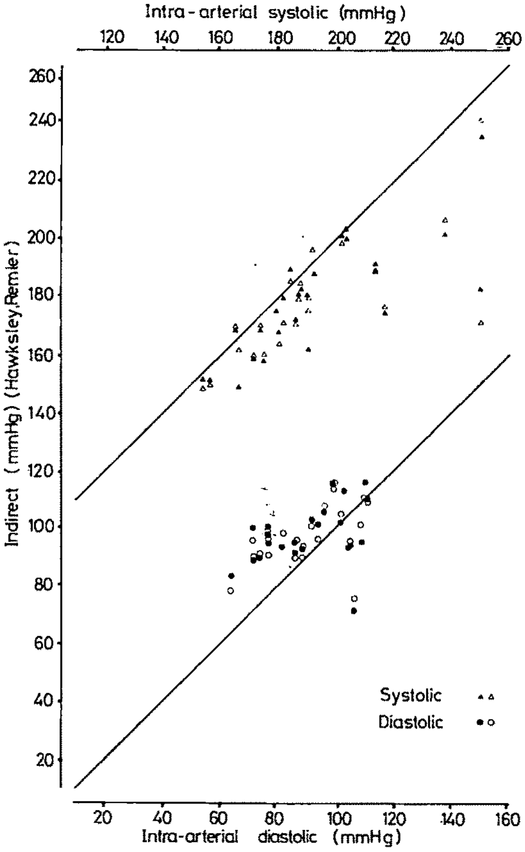

Fig. 5 *Comparison of Remler and Hawksley recordings with intra-atrial recordings. Lines of identity are given. Remler recordings are indicated by the closed symbols and Hawksley recordings by the open symbols.*

radial artery through a Bell and Howell pressure transducer on to light sensitive paper (Fig. 3c). Three recordings were made in each patient as not all Remler recordings would be decodable.

The relation between Remler and intra-arterial recordings was the same as between Hawksley and intra-arterial recordings for both systolic and diastolic blood pressures (Fig. 5, Table 4). Again, there was no significant difference between Hawksley and Remler recordings.

RELIABILITY STUDY

The reliability of the Remler in recording ambulatory blood pressure was assessed by determining the number of decodable recordings from 69 attempted Remler ambulatory day recordings. Of these, five failed completely, in three cases because the microphone lead broke and in two because of a defect in the "off" pressure switch which failed despite normal deflation. In the remaining 64 tapes, 1129 pressure recordings were attempted and 104 (9·2%) of these were undecodable. In 35 (3·1%) this was because of the failure of the microphone to detect any sounds and in the remainder because of either incorrect setting of the on-off pressure switches or patient movement.

In 13 hypertensive patients the reliability of Sphygmolog ambulatory recordings was compared with that of Remler ambulatory recordings. Recordings with each device were carried out in each patient on separate days during normal daily activities. The order of machines was randomised to prevent a training effect and treatment between the two days was not altered.

In only five of 13 Sphygmolog day recordings could a reasonable attempt be made at analyses compared with 12 of 13 Remler day recordings (X^2 5·42 after Yates correction, p<0·02). In the remaining eight, there were no decodable recordings. In six cases this was the due to dislodgement of the paper disc from the motor spindle and in two a large number of artefacts made decoding impossible. The one Remler failure resulted from an excessive cuff deflation rate.

INTEROBSERVER VARIABILITY IN DECODING

Interobserver variability in decoding was assessed by comparing the decoded results of two observers for 120 Remler and 88 Sphygmolog blood pressure recordings made in the laboratory.

There was no significant difference between the two observers in decoding Remler recordings, but 10% of all decoded recordings differed by more than ±5 mmHg, the mean difference being 0·7±4·2 mmHg for systolic and 0·6±5·4 mmHg for diastolic blood pressure recordings. The paired decoded recordings were highly correlated for systolic (r, 0·99, p<0·001) and diastolic (r, 0·93, p<0·001) recordings. Similarly, there was no significant difference between observers for decoding Sphygmolog systolic recordings though there was a small difference for diastolic recordings, the mean being 1 mmHg (p<0·01). The paired decoded recordings were again highly correlated for both systolic (r, 0·98, p<0·001) and diastolic (r, 0·99, p<0·001) pressures. Of the 88 paired decoded recordings, 9·2% of systolic and 5% of diastolic recordings differed by more than 5 mmHg.

Discussion

Accuracy studies of automated blood pressure recorders are beset with problems, including the variation between repeated blood pressure measurements, interdevice variability,[11] observer error,[14] and the type of standards against which they should be tested.[15 16] Where it is possible, as for these two machines, to apply both the standard and automatic recorders to the same brachial artery, comparison of simultaneous recordings in the same arm is the ideal method of assessment.[17] This removes the effect of blood pressure variability, which may otherwise be ascribed to the method of blood pressure recording under test. Furthermore, by comparing the recordings of a number of test instruments made repeatedly in a small group of patients, interdevice differences are easily detected which would otherwise require recordings from large numbers of subjects. Simultaneous mercury sphygmomanometer recordings can be used as a standard against which these differences are confirmed, excluding blood pressure variability as a possible cause.

The accuracy of the Remler M2000 has been assessed previously with varying results.[18-22] In two studies in which the standard used for comparison was the LSH sphygmomanometer, the Remler was found to over-

Table 4 *Comparison of mean Remler, Hawksley, and intra-arterial recordings in each of 23 patients*

	Systolic (mmHg)					*Diastolic (mmHg)*				
	Remler		*Intra-arterial*		*Hawksley*	*Remler*		*Intra-arterial*		*Hawksley*
Mean ± SEM	177·2±4·3		190·6±5·7		178·3±4·4	98·1±2·1		98·5±3·0		97·8±2·0
Mean difference (indirect vs direct)		−13·4**		−12·3**			+8·6**		+8·3**	
Correlation coefficient		0·78***		0·73***			0·4		0·51*	

*p<0·05, **p<0·01, ***p<0·001.

estimate systolic and diastolic blood pressures.[18 20] In contrast, when compared with the Hawksley[22] or a standard mercury sphygmomanometer,[19] the Remler showed no mean bias. In this study the Remler recordings were higher than simultaneous LSH sphygmomanometer recordings, whereas there was no difference between Remler and Hawksley recordings. This is consistent with our previous finding that the LSH sphygmomanometer underestimates blood pressure partly because of incorrect calibration but also because of an interpretative difference between the LSH sphygmomanometer and other methods of blood pressure measurement.[23] The interpretative difference results in an error during blood pressure recording which is heart rate dependent[23] and is confirmed in this study by the negative correlation between the mean Remler-LSH sphygmomanometer differences for diastolic blood pressure and heart rate.

Comparison of Remler and intra-arterial recordings has shown a systematic error of +3/+2 mmHg.[21] The relation of indirect to intra-arterial measurement, however, is highly variable.[24-26] Therefore, comparison of Remler and intra-arterial recordings should be assessed by simultaneous comparison of Remler and mercury sphygmomanometer recordings with intra-arterial recordings. In this study the mean bias and relation between direct and indirect recordings was the same for Remler and Hawksley recordings.

A possible source of variability and bias in Remler recordings is the interobserver difference in the decoding process. Though no significant difference was found between observers, decoded results could differ by more than 5 mmHg in 10% of recordings. This may partly explain the scatter of Remler recordings when compared with standard mercury sphygmomanometer recordings.[23] This interobserver variability, however, is no greater than for standard sphygmomanometer recordings.[15]

The reliability of Remler ambulatory recordings is reduced to a large extent by defects in the microphone lead. This also reduces the availability of the recorder as broken microphones must be returned to the manufacturer for repair, and recorders may lie idle for some time.

The Cardiodyne Sphygmolog is the simplest and most inexpensive complete ambulatory blood pressure system available. Though on the market, it has not been previously evaluated. Accuracy studies showed that the Sphygmolog tended to underestimate diastolic pressure when compared with the Hawksley random-zero sphygmomanometer. This difference, however, was small, and overall this device was reasonably accurate. Interdevice variability studies showed that one recorder gave higher recordings than the two other devices tested. This was the result of a zero drift of 3 to 4 mmHg in the pressure transducer.

Reliability of the Sphygmolog recorder was low. This was not the result of poor technique by the patients as recordings with the Remler M2000 were successful. The main defect, which appears easily correctable, is that the recording discs are displaced from the motor spindle when the machine is in the upright position during ambulatory recording. Even if this were corrected, however, there were a large number of artefacts in two of the remaining day recordings. This may be because of oversensitivity of the recording system, which would explain the tendency to underestimate diastolic pressure, and the absence of any system in the recorder for artefact suppression. Artefactual recording is a major problem during automated blood pressure recording,[27] the commonest cause being movement of the patient's arm. This may be overcome by either using appropriate band filters,[28 29] so that only sounds with the frequency characteristics of Korotkoff sounds[30] are recorded, or by recording sounds occurring within a short period after the QRS complex of the electrocardiogram.[8 31-33] With some systems[7 34] the observer analyses the recorded data and artefacts are rejected on the basis of the occurrence of sounds in an expected position or sequence, or by rejecting recordings altogether as undecodable. In contrast, the permanent record of the pressure measurements made by the Sphygmolog gives no indication whether pen marks are the result of Korotkoff sounds, arm movement, or extraneous sounds.

In conclusion, the Remler M2000 semiautomatic portable recorder is accurate in the measurement of blood pressure. Differences in the findings of previous studies can be explained by the different standards used for comparison. The reliability of the Remler M2000 could be improved by strengthening the microphone lead attachment to the microcassette recorder. The Sphygmolog is a reasonably accurate though unreliable method of recording ambulatory blood pressure. Reliability is poor mainly because of a defect in the method used to retain the paper discs on the revolving spindle of the motor. The Cardiodyne Sphygmolog, as presently designed, cannot be recommended for ambulatory blood pressure monitoring.

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Normal coronary arteriogram
An avoidable test?

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SUMMARY Between 10 and 20% of coronary arteriograms in patients with chest pain show normal vessels, often in association with a history of "atypical" angina. Conventional non-invasive tests are inaccurate in this group of patients compared with those with classical angina. This study prospectively evaluates combined 12 lead exercise electrocardiography and thallium-201 scintigraphy as a screening test in patients with atypical angina in order to determine whether normal arteriograms are avoidable in this important subgroup of patients presenting with chest pain.

Sixty seven consecutive patients with atypical angina underwent both maximal exercise testing and thallium scintigraphy before coronary arteriography. Chest pain during exercise was a poor predictor of coronary disease in this group. Eleven (16%) had abnormal arteriography, with the sensitivity of exercise and thallium tests being 45% and 73%, respectively. When both tests were applied the predictive accuracy for normal coronary arteries was 96% (54/56) and that for the presence of coronary disease was 82% (9/11).

If coronary arteriography was withheld in patients in whom both the exercise test and thallium scintigraphy were negative, the number of normal coronary arteriograms could be reduced with only a very small risk of failing to detect individuals with coronary disease.

Coronary arteriography is widely used in the assessment of patients with chest pain though a significant proportion undergo this investigation solely to establish whether or not coronary artery disease is present. At the London Chest Hospital, for example, excluding patients with valvular heart disease and cardiomyopathy, 380 (16·6%) of 2292 coronary arteriograms performed in the years 1977–79 were normal. Within this group there was a preponderance of patients with atypical angina. There remains a need for non-invasive techniques that can accurately assess the presence or absence of disease in this difficult group of patients, thereby diminishing the use of diagnostic coronary arteriography, and avoiding the small risk involved in such a procedure.

Our early experience of exercise electrocardiography and exercise thallium-201 scintigraphy in patients with coronary disease suggested that a combination of these methods might provide a useful screening test.[1] The predictive accuracy of a single diagnostic test diminishes as the disease prevalence within the population under study falls.[2] It is only by the combination of two tests, ideally looking at different but related indices for ischaemia, that a high predictive accuracy could theoretically be maintained. This study was established to assess the ability of combined 12 lead exercise testing and thallium-201 scintigraphy to predict those patients with normal coronary arteriography within a group presenting with atypical angina.

Subjects and methods

Sixty seven consecutive patients complaining of atypical angina were studied. They comprised 56 men and 11 women aged 29 to 62 years (mean age 49 years). Patient selection was prospective before the results of any non-invasive test were known. Patients with classical angina (exercise related chest pain, relieved by rest and trinitrin and exacerbated by cold or emotional stress) were excluded, as were those with a history of previous myocardial infarction or definite non-cardiac chest pain. The remaining patients had "atypical" angina defined as follows: the chest pain was thought to be anginal by the referring physician though either there was no apparent relation of pain to exercise or it was not immediately relieved (within 10 minutes)

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by rest or trinitrin. None of the patients had been investigated, other than by a resting electrocardiogram, before referral. Routine treatment consisted of a beta blocking agent in 48 (72%), long acting nitrates in 22 (33%), and a calcium antagonist in 13 (19%). Fifty nine (88%) were taking trinitrin as necessary.

EXERCISE TEST

Each patient underwent maximal 12 lead treadmill exercise electrocardiography using a modified Bruce protocol.[3] The 12 leads were the same as those recorded in a standard electrocardiogram. Recordings were made on an automated three channel machine at rest, at the end of each three minute stage, at peak exercise, and at two minute intervals during the recovery period until the electrocardiogram returned to the resting state. Blood pressure was monitored at the end of each stage. End points for the test were chest pain, dyspnoea, achievement of predicted maximum heart rate (220-age), or inability to continue exercise because of fatigue or calf claudication.

THALLIUM SCANNING

Thirty seconds to one minute before the attainment of peak exercise 2 mCi of thallium-201 was injected via an antecubital vein. Five minutes after exercise the patient was positioned in front of a Searle LFOV gamma camera or a Nuclear Enterprises MkV HR gamma camera, interfaced with a Searle Scintiview processing system or a Varian V76 computer, respectively. Scans were obtained in the 45° left anterior oblique, left lateral, and anterior views with 300 000 counts recorded for each frame. The images were processed by a combination of nine point smoothing and background subtraction. Abnormal perfusion was defined by segmental uptake of less than 50% that found in the most active myocardial segment.

INTERPRETATION OF RESULTS

All patients underwent coronary angiography with multiple views obtained using the Sones technique. Lesions of 70% or more stenosis in a major coronary artery were considered significant. Exercise electrocardiography, thallium scanning, and coronary angiography were all examined and reported separately without knowledge of the other results.

Results

Eleven (16%) of the 67 patients had an abnormal coronary arteriogram. Six patients had disease in one artery and only two had triple vessel disease. All the women had normal coronary arteriography.

The resting electrocardiogram was abnormal in 25 (37%). Nineteen of these had normal coronary arteriography. The resting electrocardiographic abnormalities, which were largely minor, are detailed in Table 1. No patients had evidence of prior myocardial infarction on the basis of pathological Q waves. The only patient with ST segment depression at rest had left ventricular hypertrophy, secondary to longstanding hypertension. An abnormal resting electrocardiogram was not associated with the presence or absence of coronary disease.

Table 1 *Resting electrocardiographic abnormalities in 67 patients with atypical angina*

Electrocardiographic finding	*No. of patients*
Bundle-branch block	2 { 1 left 1 right
Left ventricular hypertrophy	1
Poor R wave progression	2
T wave "abnormalities"	20

EXERCISE TEST

Although chest pain on exertion was a feature of the history of most patients in this study, only seven (10%) developed chest pain during the exercise test, and six of these had normal coronary arteriography.

Seven (10%) patients had an unequivocally positive exercise electrocardiogram when using 0·1 mV horizontal or down sloping ST segment depression from rest at 80 ms after the J point as the diagnostic criterion. With 0·2 mV of ST depression the number of positive tests was six. Five (71%) of the seven patients with exercise-induced ST depression had coronary artery disease. Of the remaining 60 patients, 51 achieved a maximal or near maximal heart rate for age without significant ST segment depression, with six (12%) subsequently proven to have coronary artery disease and thus falsely negative exercise tests. In the remaining nine patients, the level of exercise was low (peak heart rate less than 105/min) because of the patients' unwillingness to proceed further. No evidence of ST depression was found and the patients were classified as negative before coronary arteriographic results were available, which confirmed that none had coronary disease.

Twelve (20%) of the 60 patients with negative exercise tests had horizontal or down sloping ST depression of greater than 0·05 mV but less than 0·1 mV, thus just failing to fulfil the "positive" criterion. Two of these had bundle-branch block and one had left ventricular hypertrophy and resting ST depression. None had abnormal coronary arteriography.

THALLIUM SCINTIGRAPHY

Satisfactory thallium scintigrams were obtained in all cases even in those with a low level of exercise. The latter were interpreted despite high background levels of activity. Nine (13%) had an abnormal scan, of whom eight had coronary disease. Three patients with coronary disease had normal scintigraphy, though all three had single vessel involvement. All five of those with double or triple vessel disease had abnormal scintigraphy. The remaining 55 patients had normal scintigraphy.

COMBINED EXERCISE AND THALLIUM RESULTS

When the results of both tests were combined for each patient nine (82%) of 11 with significant disease were identified. In the two patients with abnormal tests but normal coronary arteriography, one had both exercise-induced ST depression and abnormal scintigraphy and the other an abnormal exercise electrocardiogram only. There was no apparent cause of the ST depression.

Both patients with coronary disease and negative tests had single vessel disease, in one an isolated occlusion of the posterior descending branch of a dominant right coronary artery and in the other a single 70% stenosis of a lateral circumflex branch. All 12 of those showing 0·05 mV to 0·09 mV ST depression had normal thallium scintigraphy and coronary arteriography.

Discussion

Patients with atypical angina are less likely to have underlying coronary artery disease than those with classical angina pectoris.[4] While normal coronary arteriography does not exclude a cardiac cause for the pain, it does provide a good long term prognosis for an individual even in the presence of continuing symptoms,[5] and will modify advice that may be given concerning the patient's occupation and life style. In the most experienced hands coronary arteriography, whether performed by brachial or femoral techniques, carries a small but definite mortality and morbidity, and it is desirable to restrict arteriography to those most likely to show coronary artery stenosis. A non-invasive test that reliably identifies patients with normal coronary arteriograms would be clinically valuable. This study was performed to test the ability of combined maximal 12 lead exercise electrocardiography and thallium-210 scintigraphy in this respect.

Only 16% of patients in this study had coronary artery disease. None of the 11 women and 20% of the men had disease. The male preponderance perhaps reflects an unwillingness of physicians to refer women with atypical pain while having a higher level of suspicion for the presence of coronary disease in men presenting with the same symptoms. Though thallium scintigraphy had a sensitivity of 73% and a specificity of 98% which was superior to the exercise electrocardiogram by itself in this study (Table 2), both tests are subject to error if used in isolation.[6]

Normal thallium scintigraphy was particularly helpful in the 12 patients in this study who had definite but less than 0·1 mV ST segment depression.[7 8]

Nine patients failed to exercise to at least 85% of the predicted heart rate maximum and thus perhaps had unreliable, though negative, non-invasive tests. None had coronary disease. A proportion of patients do find exercise tests formidable and are unwilling to perform an adequate test. Such patients must be assessed on an individual basis and either have a second exercise test or proceed to arteriography. Patients with angina who are unable to exercise to rapid heart rates are more likely to have coronary disease even without ST segment change,[9] but these data cannot be used automatically to justify arteriography in patients with atypical angina.

Patient selection for this study is of critical importance in assessing its value. Patients were evaluated prospectively on the basis of the clinical presentation and resting electrocardiogram without any non-invasive testing before inclusion in the study. We deliberately excluded those with a high likelihood of disease (typical angina and prior myocardial infarction) and the study group was obtained consecutively from routine new patient referrals from general practitioners and non-specialist physicians. In retrospect, if only those patients with positive (11 patients) or equivocal tests (the 12 patients with 0·05 mV to 0·09 mV ST depression) underwent angiography then all those with multivessel disease were identified, with the prevalence of disease in this selected group being significantly higher than in the remaining patients (prevalence 39% (9/23) versus 5% (2/44), $p<0{\cdot}0125$). The clinical impact of such an approach can only be assessed from the results of a larger scale study than this one. Nevertheless the results are encouraging and suggest that

Table 2 *Results of each investigation and combined interpretation**

Test	*True positive*	*False negative*	*True negative*	*False positive*	*Sensitivity*	*Specificity*	*PA+*	*PA−*
Thallium-201	8	3	46	1	73%	98%	89%	94%
12 lead exercise	5	6	45	2	45%	96%	71%	88%
Thallium or exercise	9	2	45	2	82%	96%	82%	96%

* Excluding the nine patients with inadequate exercise (peak heart rate 105/min).
Sensitivity, % positive/number with coronary disease; Specificity, % negative/number with normal coronary arteries; PA+, predictive accuracy of a positive test; PA−, predictive accuracy of a negative test.

about half of the normal coronary arteriograms currently performed are perhaps avoidable.

The coronary arteriograms were assessed only for the presence of fixed lesions and no attempt was made to detect coronary artery spasm. The object of this study was to determine whether a normal coronary arteriogram could be predicted, not to establish the cause of the presenting symptom. Ergometrine provocation testing was abandoned in our unit in 1979 in view of the risk of myocardial infarction and death resulting from such tests.[10] We have not excluded spasm, therefore, as a cause of the pain in some of our patients.

The relatively poor predictive accuracy of the exercise electrocardiogram in patients with atypical angina is in accord with previous studies.[4 11] Exercise is an integral part of thallium scintigraphy and both electrocardiogram and scintigram provide complementary information in the overall assessment of an individual patient with chest pain. This study has confirmed that if coronary arteriograms are withheld in those with normal non-invasive tests there is only a small risk to detect an individual with coronary stenosis.

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Sinus node function in first three weeks after cardiac transplantation

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SUMMARY Donor sinus node function was studied in 10 patients from day 4 to day 24 after cardiac transplantation. Cycle length, atrial arrhythmias, corrected sinus node recovery time, and estimated sinoatrial conduction time were recorded daily. Five patients had at least two sets of results suggesting sinus node dysfunction (group A) while five patients had no such abnormalities (group B). The prognosis in group A was poor, with four of the five patients dying within four months of the operation; one unexpected death from arrhythmias was recorded by ambulatory electrocardiographic monitoring. All five patients in group B survived for at least eight months. In nine patients sinus node function varied from day to day, with corrected sinus node recovery time reaching a peak at 11 to 18 days after operation. The longest corrected sinus node recovery time was 11 160 ms. Neither the differences between the patients, nor the day to day variation, could be explained solely by the degree of rejection as assessed by biopsy or by the ischaemia time of the heart during procurement. Sinus node dysfunction soon after transplantation is associated with a poorer prognosis and might be the terminal event in some cases.

After cardiac transplantation the new heart remains isolated from the autonomic nervous system.[1 2] Several studies have explored the function of the human sinus node in this unusual state.[2–6] These investigations have all been on patients who have survived at least a year after the operation and have no evidence of rejection in a simultaneous myocardial biopsy. Thus sinus node function has been studied only in a selected group of patients who have survived for some time after the operation.

The first five patients to receive a heart transplant at Papworth Hospital, Cambridge, had an unexpectedly high incidence of sinoatrial arrhythmias in the immediate postoperative period. We therefore undertook a prospective study of sinus node function during the first three and a half weeks after transplantation. The first aim was to explore the effects of the operation on the human sinus node. The second was to assess whether sinus node function would provide a guide to the immunological state of the rest of the heart.

Patients and methods

Eleven consecutive patients undergoing cardiac transplantation were studied. One patient developed fits and unconsciousness one week after the operation, which prevented further testing. The rest of this report is concerned with the remaining 10 patients. They were all men, aged from 22 to 52 years (mean 40).

The donor hearts were all brought to Papworth from other hospitals. Immediately before removal from the donor they were perfused with a cardioplegic solution at 4 C containing procaine and a high concentration of potassium and magnesium (Table 1). The hearts were transported at about 4 C, eight in cardioplegic solution and two in Ringer's solution. The ischaemia times of

Table 1 *Papworth Hospital cardioplegic solution*

Ions	*mmol/l*
Mg	16
Na	149
K	20
Ca	2
Cl	172
HCO_3	10
Procaine	1·2

pH 7·4
Osmolarity 340 mOsmol/kg H_2O

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Table 2 *Drug treatment during study period*

(1) Prednisolone 1 mg/kg per d
(2) Azathioprine 1·5–2·5 mg/kg per d
(3) Antihuman thymocyte globulin (ATG) 250–1000 mg/d
(4) Cimetidine 1g/d
(5) Hydrochlorothiazide 25–50 mg/d
(6) Triamterene 50–100 mg/d
(7) Amphotericin throat lozenges

the donor hearts ranged from 113 to 190 minutes (mean 158). The hearts were inserted by the techniques developed at Stanford University Medical Centre.[7] The donor right atrium is sutured to the posterior and lateral walls of the recipient right atrium so that blood can drain from the recipient's vena cavae into the donor right atrium. The donor sinus node is protected by ligating and dividing the donor superior vena cava 1·5 cm above the cavoatrial junction. At the end of each operation two epicardial wires are applied to the donor right atrium.

Sinus node function was assessed daily from postoperative days 4 to 24. This period was chosen because some of the patients received isoprenaline infusions during the first three days and the atrial wires were removed soon after the 24th day. The routine postoperative care at Papworth Hospital has been described previously.[8] The drug treatment during the study period is shown in Table 2. No digoxin or other antiarrhythmic drugs were given to these patients.

The tests of sinus node function were selected so that they could be performed easily with simple, sterilisable, equipment in the intensive care area. Testing was carried out in the middle of the morning after 10 minutes bed rest. The temporary epicardial wires were used for bipolar atrial pacing, with measurements being taken from the external P waves. The stimulus strength was twice the threshold value, with a pulse width of 1 ms. The spontaneous cycle length of the donor atrium was recorded. This varied little in the denervated heart with the patient at rest. The sinus node recovery time was found by pacing for one minute at 100, 110, 120, and 130 beats per minute or 110, 120, 130, and 140 beats per minute if the spontaneous rate was above 100 per minute. On each occasion the spontaneous cycle length was subtracted from the recovery time to give the corrected sinus node recovery time. The estimated sinoatrial conduction time was calculated by a method similar to that described by Narula and colleagues.[9] For this the atrium was paced for nine cycles at a rate 10 beats per minute faster than the spontaneous rate. The sinoatrial conduction time, that is the estimated conduction time into and out of the node, is the duration of the first post-pacing cycle minus the duration of the last spontaneous cycle before the onset of pacing. The spontaneous cycle varied little, so a single measurement was used rather than the mean of a number of cycles. On each occasion the sinoatrial conduction time was measured five times and the mean value calculated.

A normal range for these sinus node tests cannot be applied to denervated hearts soon after operation. But in other patients in our hospital the normal upper limit of the corrected sinus node recovery time is 525 ms and the sinoatrial conduction time is 250 ms. The cycle length of a transplanted heart one year or more after operation is normally less than 800 ms.[1 6]

Results

The 10 patients showed a wide range of results and could be divided into two groups on the basis of the maximum values recorded during the study period (Table 3). The five patients in group A had pacing results outside our normal values for innervated hearts, atrial tachycardias, or a maximum cycle length above 1000 ms. All patients in this group had at least two of these features. The recovery time could be grossly abnormal. Fig. 1 shows a 12 second pause on cessation of pacing in case 2. In contrast, the other five patients (group B) all had corrected recovery times below 525 ms, sinoatrial conduction times below 250 ms, and

Table 3 *Sinus node function tests in the 10 patients*

	Max CL (ms)	*Max CSNRT (ms)*	*Postop day for max CSNRT*	*Max SACT (ms)*	*Postop day for max SACT*	*Atrial tachycardia during study period*	*Outcome*
Group A							
Case 1	1020	835	12	279	12	–	Alive at 27 months
Case 2	1240	11 160	12	248	5	–	Died at 10 weeks
Case 3	890	615	15	350	10	–	Died at 18 weeks
Case 4	1005	1020	18	145	18	+	Died at 8 weeks
Case 5	1100	1240	13	313	18	+	Died at 7 weeks
Group B							
Case 6	780	230	14	130	9	–	Alive at 23 months
Case 7	890	450	16	173	16	–	Alive at 21 months
Case 8	920	430	17	140	14	–	Alive at 20 months
Case 9	770	390	11	145	11	–	Died at 9 months
Case 10	670	165	a	125	a	–	Alive at 15 months

Max CL, maximum cycle length; max CSNRT, maximum corrected sinus node recovery time; max SACT, maximum estimated sinoatrial conduction time; a, no day to day variation.

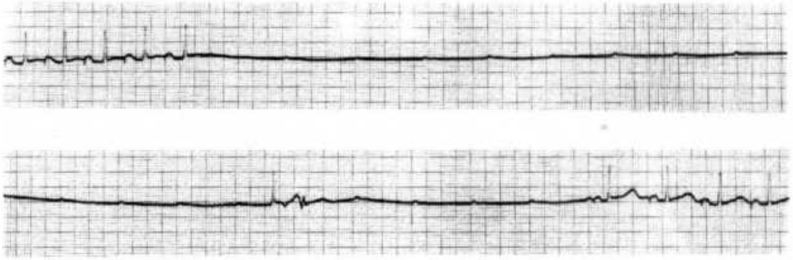

Fig. 1 *Continuous recording of lead 2 (25 mm/s) in case 2 showing 12 seconds of asystole after cessation of pacing. Atrial pacing is switched on again at the end of the trace. The activity of the recipient atrial remnant can be seen during the period of asystole of the donor atria and ventricles.*

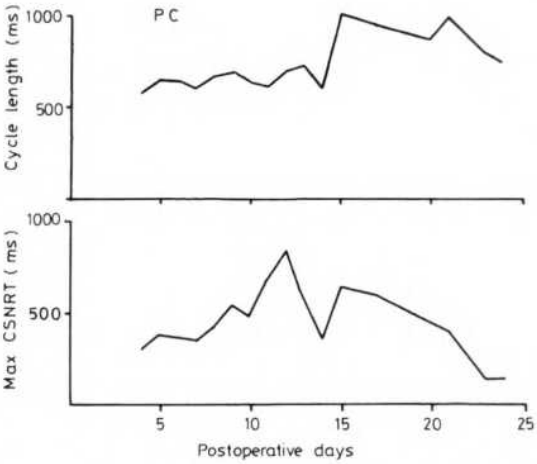

Fig. 2 *Cycle length and maximum corrected sinus node recovery time on each day in case 1.*

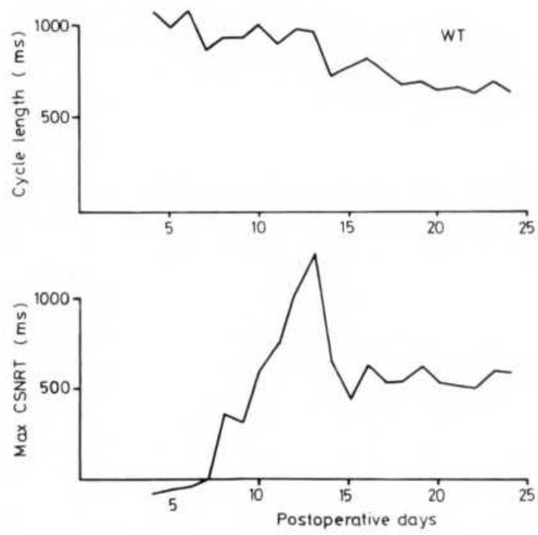

Fig. 3 *Cycle length and maximum corrected sinus node recovery time on each day in case 5.*

cycle lengths below 1000 ms on each day. No atrial arrhythmias were seen in this second group during the study period.

In nine of the 10 patients considerable day to day variation occurred in the tests. The corrected recovery time lengthened progressively up to a maximum at 11 to 18 days followed by a shortening (Table 3, Fig. 2 and 3). The conduction time in these patients also reached a peak at 5 to 18 days and then fell.

The cause of the difference in results between the two groups and the day to day variability was not clear. The changes did not correlate with the degree of rejection as assessed by endocardial biopsy. For example, biopsies on days 10 and 23 from the patient whose results are illustrated in Fig. 2 were normal. Biopsies from the patient illustrated in Fig. 3 showed no rejection on days 11, 21, and 31. In contrast, case 9 had severe rejection on day 8 but the sinus node function testing was unremarkable throughout. Nor were conduction abnormalities related to a longer ischaemia time of the donor heart at the time of transplantation. The mean time in group A was 146 minutes and in group B it was 169 minutes. Day to day variations in plasma sodium or potassium concentrations had no noticeable influence on sinus node function.

The subsequent progress of the patients in group A was poor. Three of the five patients died during episodes of rejection at seven, eight, and 10 weeks after operation. One of these deaths was an unexpected cardiac arrest at another hospital while undergoing preliminary assessment for suspected rejection. Another patient in this group (case 3) died unexpectedly during electrocardiographic monitoring at our hospital. The remaining patient is well two years after the operation and has had no demonstrated arrhythmias.

In contrast to these poor results the five patients in group B all survived eight months and four are alive 15 to 23 months after the operation, though case 6 was paced prophylactically at five months after asymptomatic atrial pauses had been seen on ambulatory monitoring. He also had one paroxysm of atrial flutter during an episode of rejection. No arrhythmias have

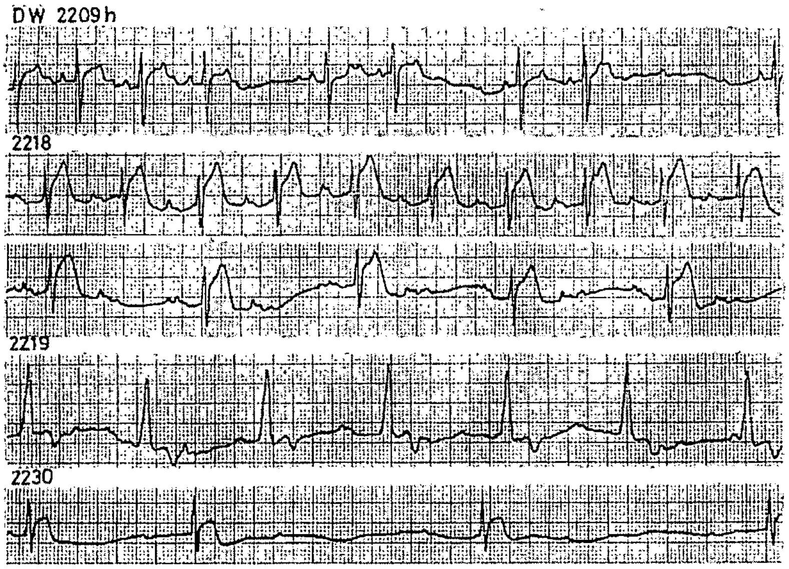

Fig. 4 *Rhythms recorded by ambulatory monitoring from case 3 shortly before his death. The top strip shows sinoatrial block followed by prolongation of intra-atrial and atrioventricular conduction in the second strip. The middle strip shows 2:1 atrioventricular block which soon changed to complete block and a ventricular escape rhythm (fourth strip). The bottom strip illustrates the terminal slow junctional rhythm which progressed to asystole. The recipient atrial remnant can also be seen in these traces.*

been seen in the other four patients in spite of at least two 24 hour periods of ambulatory electrocardiographic monitoring. Case 9 died from acute rejection at nine months.

Case 3, who died during ambulatory monitoring, had been shown to have asymptomatic atrial pauses six weeks before his death. At that time they were not thought to be important. When he was admitted for a routine endocardial biopsy four months after the operation, the opportunity was taken to perform a further 24 hour tape. At this time he was well and had already returned to part-time work. He was found dead in bed early the next morning with the recorder still running. The tape showed that about 20 minutes after he went to bed he began to develop periods of sinoatrial block (Fig. 4). A few minutes later prolongation of both intra-atrial and atrioventricular conduction was seen. Second degree atrioventricular block soon followed. A minute later he was in complete atrioventricular block with an escape rhythm probably of ventricular origin. This reverted to a junctional rhythm which became slower and slower until asystole occurred 10 minutes later. Necropsy examination showed a moderate degree of rejection.

Discussion

This study has shown a high incidence of sinus node dysfunction in the first few weeks after cardiac transplantation. The abnormalities described seem to be associated with a poor prognosis as only one of the five patients affected survived more than four months after the operation. The low incidence of sinus node disorders reported in earlier studies may have resulted from investigating patients a year or more after operation; the patients with abnormalities may not have survived for this length of time. Another possibility is that the dysfunction is temporary. This study was not designed to test these theories.

The cause of this sinus node dysfunction remains uncertain. One possibility is surgical trauma to the node or its blood supply. All operations were done by the same surgeon and care was taken to prevent any trauma to the donor heart in the region of the superior vena cava/right atrial junction. Surgical techniques were identical in the two groups, as were the drugs used.

Another explanation could be that the sinus node was abnormal before removal from the donor. The electrocardiograms taken at this time show no evidence of sinus node dysfunction. The period of ischaemia while the heart is transported and inserted into the patient could be the cause of the nodal disorders. Damage to the heart occurs during this period but it is reversible.[10] The sinus node may be more resistant to the protective effects of cold cardioplegic solution than the rest of the heart.[11] But longer ischaemia times were not associated with sinus node dysfunction. The mean ischaemia time in those patients without abnormalities (group B) was slightly greater than in those with dysfunction (group A). The differences in sinus node function, however, could be produced by more subtle variations in the preservation technique.

Other reports have implicated acute rejection as the main cause of atrial arrhythmias in both dogs[12 13] and humans[14–16] after transplantation. In this study rejection as assessed by biopsy did not discriminate between patients who developed abnormalities and those who did not. In addition, the degree of rejection did not explain individual day to day variations in the tests. On the other hand, an immunological mechanism might have a maximum effect about two weeks after the operation and the nine patients with considerable variation all had a maximum corrected sinus node recovery time between 11 and 18 days after transplantation. Immunological events undetected by biopsy could be important. But such a mechanism could not be the sole cause of the dysfunction as abnormalities could often be detected right at the beginning of the study period on day 4; rejection would take longer to develop.

The sinus node dysfunction is probably the result of a combination of factors. The initial event could be ischaemia at the time of transplantation. Subtle forms of rejection might then limit healing or produce further damage. This type of explanation would account for the poorer prognosis in these patients. Animal studies and detailed electrophysiological investigations of long-term survivors are being undertaken to try and elucidate the problem.

Whatever the cause of the sinus node dysfunction, the death of one patient during ambulatory monitoring illustrates that pacemaker tissue disorders are important after cardiac transplantation. In the general population sinus node dysfunction is a common cause of symptoms but is rarely fatal.[17-19] The subsidiary pacemakers in the innervated heart will provide some form of escape rhythm. Such rhythms seem less reliable in these denervated hearts. Recognised causes of death after cardiac transplantation do not include cardiac arrhythmias.[20] But arrhythmias cannot be diagnosed at necropsy. The terminal event in some cases could be severe sinus node dysfunction.

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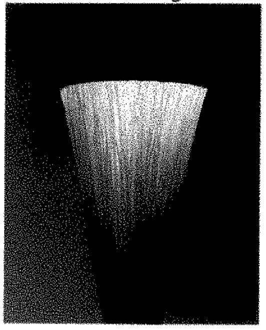

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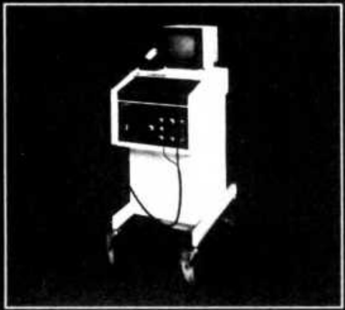

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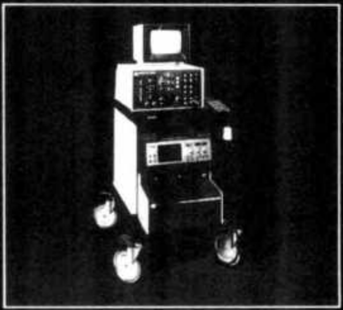

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Irreversible morphological changes contributing to depressed cardiac function after surgery for chronic aortic regurgitation

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SUMMARY The timing of surgery in chronic aortic regurgitation remains a difficult problem. To identify variables predictive of postoperative haemodynamic improvement, changes in left ventricular mass, volume, morphology, and histochemistry were analysed in 67 patients undergoing surgery for chronic aortic regurgitation. Patients were divided into two groups: those in whom the left ventricular echo diameters returned to normal after operation (51 patients, group A), and those with postoperative dilatation (16 patients, group B). A preoperative biopsy was obtained in all patients; postoperative tissue samples were available in 13 patients (five from group A, eight from group B). Data were correlated with the postoperative clinical, haemodynamic state over a follow-up period of three years. Regression of hypertrophy was usually incomplete. Echocardiographic and angiographic data could not define the type and degree of dysfunction which was irreversible. Massive fibre hypertrophy (mean 34·1 μm), moderately or severely increased interstitial fibrous tissue, reduced levels of the myofibrillar and mitochondrial enzymes adenosine triphosphates and succinate dehydrogenase in pre- and postoperative tissue samples correlated with persistent dilatation, cardiac failure, and early death (group B).

Irreversible morphological and functional changes contributed to a depressed cardiac function after operation. Preoperative ventricular biopsies are thus of prognostic importance in volume overload.

Patients undergoing aortic valve replacement for volume overload generally experience haemodynamic improvement and relief of presenting symptoms. In some instances, however, surgical correction does little to alter the course of the disease.

The extent to which clinical improvement is associated with regression of hypertrophy and abnormalities of ventricular function is not well known.[1 2] In this study we analysed the changes in ventricular mass, volume, and histochemistry in a selected group of patients who underwent homograft aortic valve replacement for chronic aortic regurgitation, correlating these changes with the postoperative clinical state. In addition, preoperative data were examined in an effort to identify variables which might predict which patients could expect a good result from surgery and which might not.

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Patients and methods

The dominant lesion requiring aortic valve replacement in all cases was chronic, severe aortic regurgitation, defined as at least grade 3/4 on angiography. Those with multiple valvar abnormalities, coronary artery disease, or combined stenosis and regurgitation were not included. There were 49 men and 18 women aged 16 to 72 (mean age 58·5 years). Aetiologies of the aortic regurgitation included non-inflammatory root disease (29 patients), rheumatic, congenital, or infective disease of the valve cusps (30 patients), and inflammatory root disease (eight patients). A pre- or intraoperative biopsy was obtained in all patients, who were also selected on the basis of technically adequate serial echocardiograms and normal prosthetic function over a follow-up period of at least three years.

POSTOPERATIVE EVALUATION

All patients were re-evaluated non-invasively (chest radiography, electrocardiography, and echocardiography) at two weeks and six months after operation; studies were then performed at yearly intervals for a minimum of three years. Three out of these 67 patients died from cardiac failure, 18, 24, and 30 months after operation, respectively. Postoperative cardiac catheterisation was performed in 21 patients in whom cardiac symptoms persisted or recurred after valve replacement. In 13 of these 21 patients left ventricular biopsy was available for comparison with the intraoperative specimen.

ELECTROCARDIOGRAPHY

Standard 12 lead electrocardiograms were obtained before and after aortic valve replacement; the Sokolow-Lyon voltage criteria and the Romhilt-Estes scores for left ventricular hypertrophy were computed.

ECHOCARDIOGRAPHY

Echocardiograms were obtained using a 12·5 mm, 2·25 MHz transducer and an Ekoline 20A ultrasound transceiver interfaced with a strip chart recorder. Echocardiographic measurement of the left ventricular transverse dimension at end-diastole, and thickness of the ventricular septum and free wall were obtained, with the ultrasound beam passing through the left ventricle caudal to the tips of the mitral leaflets, taking the peak of the R wave as end-diastole. Because of changes in septal motion after aortic valve surgery, end-systolic dimensions were not analysed. From the primary echocardiographic measurements, the left ventricular cross-sectional wall area was used as an estimate of left ventricular mass.[3] Estimates on normal subjects were 16±4 cm^2.

This cross-sectional area is useful for the serial assessment of left ventricular hypertrophy but assumes uniform distribution of the muscle mass around the ventricular circumference.

CARDIAC CATHETERISATION

Twenty-one patients underwent postoperative cardiac catheterisation. Recurrence of cardiac symptoms, and persistent cardiomegaly were the most frequent indications for the repeat studies. Ventricular function was assessed before and after valve replacement in all 21 cases using computerised, quantitative, radial analysis of segmental wall motion derived from the single plane left ventricular cineangiogram.[4]

BIOPSIES

Biopsy material was available before valve replacement in all 67 patients, the tissue being obtained either from preoperative endomyocardial biopsies or from an intraoperative biopsy. In 15 of these patients the biotome tissue samples were also compared with an operative specimen, to establish whether the smaller bioptome samples were representative of the rest of the myocardium. Postoperative left ventricular biopsies were also available from 13 patients for comparison with the preoperative specimen. The endomyocardial biopsies were obtained with the modified Olympus fibreoptic bronchoscopic biopsy forceps introduced using the long sheath technique.[5] Specimens were taken from the free wall of the left ventricle towards the apex; four to six tissue samples were obtained in each case. The intraoperative full thickness specimens were taken before cardiopulmonary bypass from the apex of the left ventricle.

HISTOLOGICAL METHODS

The left ventricular biopsy material was divided; one half was paraffin embedded, and 5 μm thick sections were stained with haematoxylin and eosin and Miller's elastic van Gieson. Hypertrophy was assessed by measuring at least 100 myocardial fibres by means of the Projectina microscope. Accurate assessment of fibre diameter was at times difficult, particularly when the interstitial fibrous tissue was severely increased. Myocardial fibre diameter was considered abnormal if it measured more than 15 μm.[6] Degenerative changes, though relatively non-specific, were also noted.

Miller's elastic van Gieson stain was used to delineate collagen tissue and other components of the interstitium.

Interstitial fibrous tissue was graded as follows:

(i) Absent – no increase in interstitial collagen tissue (Fig. 1).

(ii) Mild – occasional foci of increased collagen tissue between adjacent myocardial fibres.

(iii) Moderate – widespread increase of collagen tissue in the interstitium not exceeding 15 μm.

(iv) Severe – widespread increase in the collagen tissue of the interstitium of 16 μm or more (Fig. 2).

Focal and confluent areas of fibrous replacement were also noted. Grades I and II were considered normal morphological alterations.

HISTOCHEMISTRY

The remaining half of the biopsy tissue was immediately frozen in "Freon" (BOC), precooled in liquid nitrogen, and stored at −70°C. Five μm thick cryostat sections were then analysed using standard enzyme histochemical methods[7 8] for myofibrillar calcium dependent adenosine triphosphatase (ATPase), succinate dehydrogenase, and glycogen.

ANALYSIS OF DATA

Postoperative observations were compared with preoperative (control) measurements using the paired Student's t test. Endomyocardial biopsy data were correlated with those obtained from the larger operative specimens in 15 cases using the coefficient of variance (expressed as a percentage).

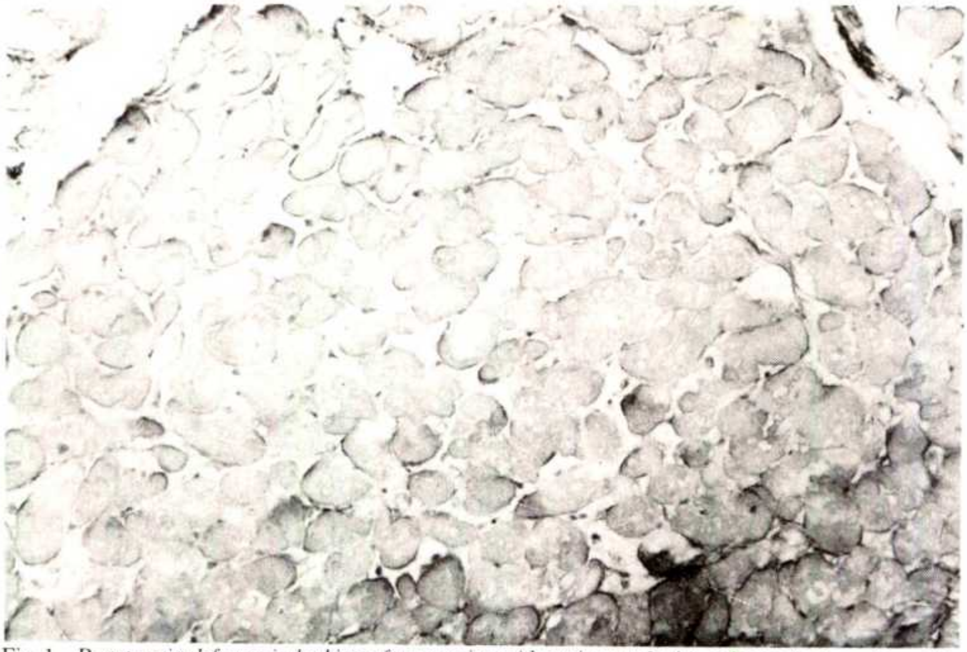

Fig. 1 *Postoperative left ventricular biopsy from a patient with aortic regurgitation and normal echocardiographic end-diastolic dimension after surgery (group A). The photomicrograph shows myocardial hypertrophy but no increase in the interstitial collagen tissue. (Miller's elastic van Gieson, original magnification ×200.)*

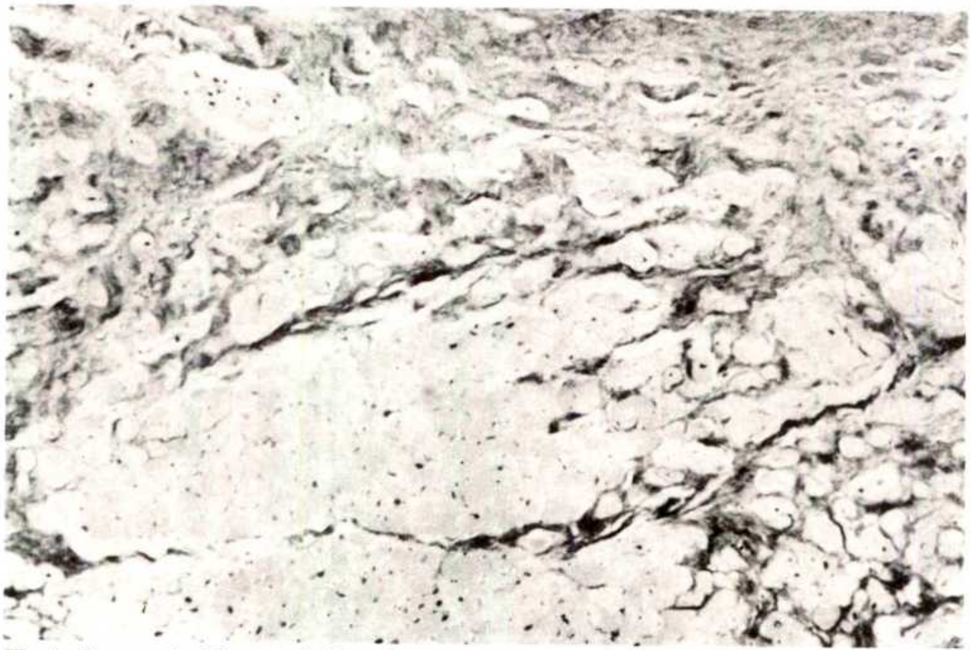

Fig. 2 *Postoperative left ventricular biopsy from a patient with aortic regurgitation and persistent ventricular dilatation despite satisfactory valve function (group B). The photomicrograph shows a severe increase in interstitial fibrous tissue as well as subendocardial confluent fibrous replacement. The mildly thickened endocardium can be discerned at the upper half of the illustration. (Miller's elastic van Gieson, original magnification ×128.)*

Results

ELECTROCARDIOGRAPHY

Of the 67 patients with chronic aortic regurgitation, 64 had electrocardiographic evidence of left ventricular hypertrophy before surgery. The voltages decreased after surgery in 50 (78%) and returned to normal in 19 of these 50 patients. Voltage changes took place within six to 12 months after operation. Of the other 17, left ventricular hypertrophy was unchanged in five patients, and nine patients developed progressive ventricular conduction abnormalities or bundle-branch block. The presence of pre- and perioperative conduction defects precluded analysis of hypertrophy in the remaining three patients.

ECHOCARDIOGRAPHY

By means of echocardiographic assessment of the left ventricular end-diastolic dimension performed at regular intervals for at least three years after operation, patients were divided into two groups (Fig. 3). Group A (51 patients) had normal end-diastolic dimensions (<52 mm) after operation (usually within three months of valve replacement); in group B (16 patients) the end-diastolic dimension remained greater than normal. Three patients in group B died in the follow-up period. Though patients in group B tended to have larger transverse dimensions before operation, there was no significant difference between the preoperative end-diastolic dimension of patients in both groups. Overall muscle cross-section area showed a gradual reduction in the first year after operation (32 ± 7 cm^2 to 22 ± 6 cm^2) ($p<0\cdot01$). Despite a decrease of more than one-third in this index of muscle mass, postoperative values were still significantly raised above the normal range at the latest follow-up ($p<0\cdot05$). The reduction of ventricular mass was paralleled by a reduction in the electrocardiographic voltages, and patients with persistently increased voltages on electrocardiographs had grossly abnormal estimates of muscle mass.

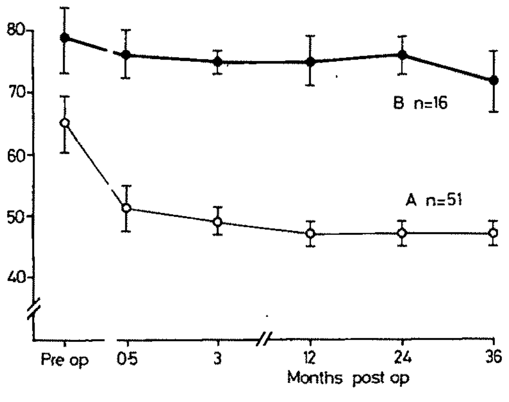

Fig. 3 *Serial pre- and postoperative echocardiographic left ventricular end-diastolic diameters (LV EDD) from the 67 patients with volume overload resulting from aortic regurgitation. Values expressed average ±SEM. Patients in group A achieved normal end-diastolic dimension after aortic valve replacement; 16 patients had persistent postoperative enlargement (group B).*

HISTOLOGY

Preoperative

Preoperative histological data are shown in Table 1. Mean myocardial fibre diameter was 26 μm for the 51 patients in group A and 33 μm for the 16 patients in group B. Abnormally increased levels of collagen (grades III and IV) were noted in only seven out of the 51 cases (13·7%) in group A; while 11 out of the 16 patients (69%) with persistent postoperative dilatation (group B) had abnormal fibrous content.

Preoperative histology was normal in 49 out of the 67 patients in this series; 44 (90%) of these 49 cases experienced postoperative clinical and echocardiographic improvement (group A), while in the other five cases the ventricular function was abnormal after valve replacement (group B). The biopsies were abnormal in 18 patients before valve replacement; operation did little to alter the course of the disease in 11 (61%) of these 18 cases.

Only a small variance was present between the histological data derived from the smaller bioptome tissue samples and those obtained from the larger operative specimens. The coefficient of variance for the 15 cases compared was 7·6%.

Postoperative

Histological data were obtained before valve replacement and on average one year after operation in 13 patients (Table 2). In this subgroup of 13 patients with biopsies before and after valve replacement, five patients had normal echocardiographic ventricular dimension after surgery (group A) and eight patients (group B) had persistent dilatation and hypertrophy. The mean muscle fibre diameter before valve replacement measured 29·3 μm in the five tissue samples from group A, and 34·1 μm in the eight biopsies from group B. This muscle fibre diameter decreased significantly to 23·4 μm in the five patients from group A ($p<0\cdot01$) but remained unchanged (32·5 μm) in the eight patients with postoperative dilatation and hypertrophy (Table 2). Those in group A had either no fibrous tissue (grade I, three cases) (Fig. 1) or mild (grade II, two cases) increase in the fibrous content in the pre- and postoperative biopsies. Moderate (grade III, four patients) and severe (grade IV, three patients) (Fig. 2) increase in fibrous tissue was documented before and after valve replacement in seven of the eight patients restudied from group B. The remaining patients from this group had grade II fibrous content.

Table 1 *Preoperative histology: 67 patients surviving aortic valve replacement, divided retrospectively into echocardiographic groups A (normal dimensions) and B (postoperative dilatation)*

		Group A (n=51)	*Group B (n=16)*
Mean myocardial fibre diameter (μm)		26	33
Interstitial collagen	Grade I to II	(44)	(5)
	Grade III to IV	(7)*	(11)*
Histochemistry	Adenosine triphosphatase (ATPase)	Normal (45), abnormal (5)	Normal (5), abnormal (11)
	Succinate dehydrogenase (SDH)	Normal (46), abnormal (5)	Normal (8), abnormal (8)
	Glycogen	Normal (48), abnormal (3)	Normal (6), abnormal (10)

*All patients with severely increased fibrous content had abnormal enzyme activity.

Table 2 *Comparison of pre- and postoperative histological and histochemical data in 13 patients with left ventricular biopsies before and after aortic valve replacement*

	Group A (n=5)		*Group B (n=8)*	
	Preoperative	*Postoperative*	*Preoperative*	*Postoperative*
Mean myocardial fibre diameter (μm)	29·3	23·4	34·1	32·5
Interstitial collagen	Grade I to II (5)	Grade I to II (5)	Grade III to IV* (7) Grade II (1)	Grade III to IV* (7) Grade II (1)
Histochemistry				
Adenosine triphosphatase (ATPase)	Normal	Normal	Normal (2), abnormal (6)	Normal (2), abnormal (6)
Succinate dehydrogenase (SDH)	Normal	Normal	Normal (3), abnormal (5)	Normal (4), abnormal (4)
Glycogen	Normal	Normal	Normal (4), abnormal (4)	Normal (4), abnormal (4)

*All patients with severely increased fibrous content had abnormal enzyme activity.

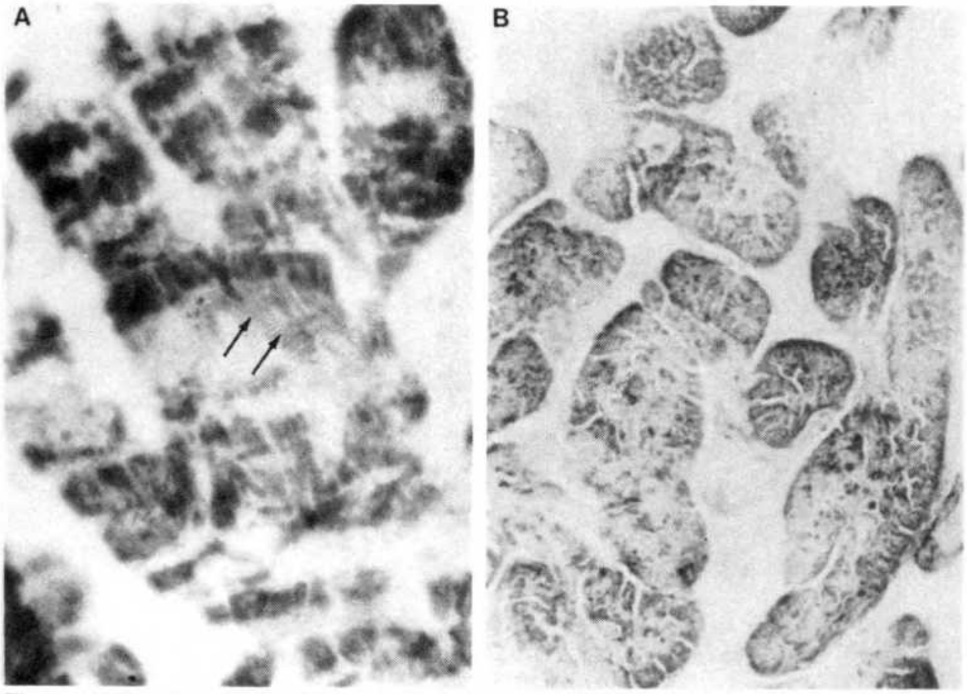

Fig. 4 *(A) Normal myofibrillar ATPase activity discretely localised on the cross-striations (arrows) in a biopsy sample from a patient with normal postoperative ventricular function and echocardiographic dimensions. (Original magnification ×800.) (B) Patchy decreased levels in tissue sample from a case of postoperative impaired contractility. The discrete localisation is destroyed and there are only coarse clumps of activity, with distorted muscle in the intervening spaces. (Original magnification ×460.) Both (A) and (B) cut obliquely.*

HISTOCHEMISTRY

Preoperative histochemical studies were normal in 45 (88%) out of the 51 biopsies from patients in group A (Table 1), and all five patients from this group who were restudied had normal enzyme activity (Table 2). Reduced levels of glycogen and of myofibril associated calcium-dependent ATPase and of the mitochondrial enzyme succinate dehydrogenase correlated with impaired ventricular function and cardiac dilatation after operation (Table 1) and one or more of these features were present in 11 (69%) out of the 16 patients in group B. Six out of the eight patients with unsuccessful outcome after surgery who were reinvestigated had reduced ATPase levels in the preoperative biopsies (Fig. 4B) and these changes persisted in the group of 13 patients studied before and after valve replacement (Table 2), decreased levels of succinate dehydrogenase were documented in five out of the 8 intraoperative samples from patients included in group B (Fig. 5B), and succinate dehydrogenase was abnormal in four of the postoperative biopsies. Persistently abnormal levels of glycogen were noted before and after operation in four patients from group B (Table 2).

All patients with abnormal histochemistry also had abnormal interstitial fibrous content (see Tables 1 and 2).

Differences in histology and histochemistry between patients included in groups A and B were not altogether clear cut, as five patients with normal biopsy studies deteriorated after operation and seven patients with abnormal levels of fibrous content and/or enzyme markers experienced clinical and echocardiographic improvement.

POSTOPERATIVE ANGIOGRAPHY

Ten out of the 21 patients restudied had normal postoperative ventricular function and these 10 cases included seven patients in whom previously impaired contractility improved significantly after surgery. The other 11 patients had large angiographic end-diastolic volumes and an ejection fraction of less than 45% after valve replacement; all these 11 cases were in the echocardiographic group B. Ventricular function and regional wall motion had either remained impaired (Fig. 6) or had deteriorated after operation in these 11 patients.

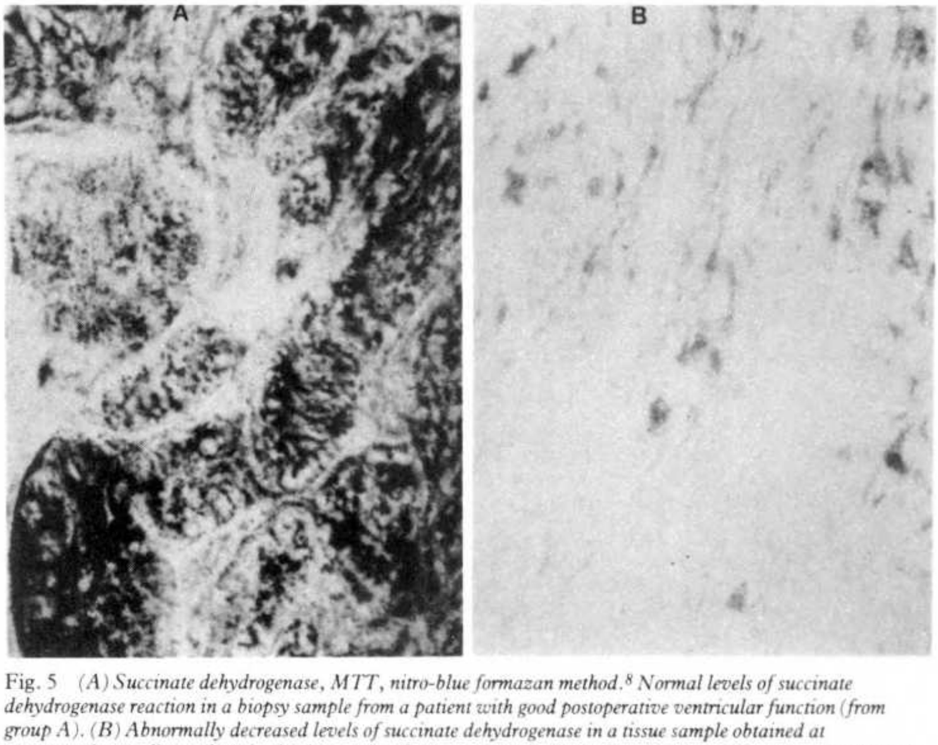

Fig. 5 *(A) Succinate dehydrogenase, MTT, nitro-blue formazan method.*[8] *Normal levels of succinate dehydrogenase reaction in a biopsy sample from a patient with good postoperative ventricular function (from group A). (B) Abnormally decreased levels of succinate dehydrogenase in a tissue sample obtained at postoperative cardiac catheterisation in a patient from group B who died a few months later from intractable heart failure two years after valve replacement in spite of satisfactory valve function. Myofibrillar staining is lost, and the reaction is confined to a few sarcosomes.*

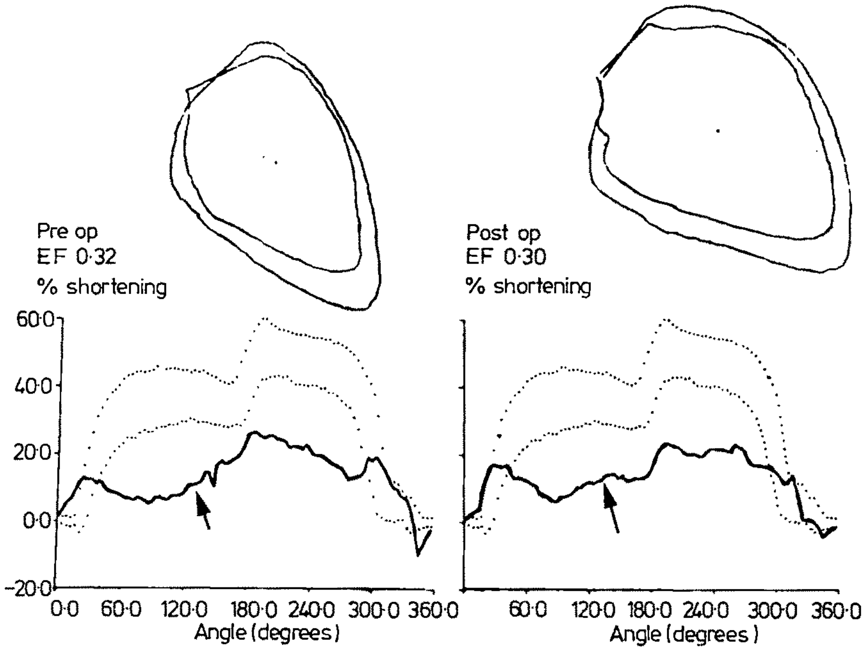

Fig. 6 *Radial analysis of segmental wall motion before (left) and after (right panel) aortic valve replacement for chronic volume overload. The bottom plots show the percentage shortening (vertical axis) against the radial angle (horizontal axis). Dotted lines represent ±SD from the mean values obtained in a group of normal patients; the arrowed line is that of a patient with aortic regurgitation and normal coronary arteries. The preoperative study (left) showed severe generalised hypokinesia; ventricular function was grossly impaired in the postoperative study (right) performed 16 months after operation, despite satisfactory valve function.*

Discussion

Aortic valve replacement in chronic volume overload usually leads to striking symptomatic and haemodynamic improvement. This is accompanied by a reduction in left ventricular hypertrophy and chamber size, and most patients achieve normal or near normal end-diastolic volumes after operation. In some instances surgical correction does little to alter the course of the disease, and these patients usually develop progressive cardiac failure. Thus, optimum timing of valve replacement in chronic volume overload is a difficult and challenging problem.[1 2]

Most of the electrocardiographic voltage changes occurred within one year of valve replacement and studies after this period showed stable voltage measurements. Our group of patients with postoperative progressive ventricular conduction abnormalities or bundle-branch block on the electrocardiogram generally had persistent ventricular hypertrophy or dilatation. These probably represented late, irreversible myocardial changes, and though some of these patients experienced clinical improvement, they were clearly at risk from subsequent death from congestive failure.

Angiography and echocardiography are the methods of choice for evaluating ventricular hypertrophy, and various studies have shown that, though considerable regression of hypertrophy occurs after aortic valve replacement, this is usually incomplete.[9-13] In our study, the difference between the patients in both echocardiographic groups (Fig. 3) could not be explained by the value of the original end-diastolic dimension. Our data suggest that preoperative echocardiography cannot define the type and degree of left ventricular dilatation and hypertrophy which is irreversible. Though some studies have suggested that patients should undergo surgery once ventricular systolic dysfunction is detected echocardiographically,[11 14] other investigators,[3 15] like ourselves, could not define this irreversible dysfunction from preoperative data.

Our angiographic studies were mostly performed in patients whose postoperative course did not follow the expected pattern, and were therefore unrepresentative of the overall group. While seven patients with abnormal preoperative haemodynamics, however, showed an improvement in ventricular function, 11 others showed either no change or a deterioration in postoperative contractility (Fig. 6). Angiographic systolic function in this series was therefore unhelpful as a predictor of postoperative haemodynamics.

The diagnostic capability of histological evaluation is well established,[16] but there are few studies correlating pathological data with clinical findings. In this study we compared the biopsy findings with clinical and non-invasive data after correction of severe chronic aortic regurgitation, to establish whether histological changes were a contributory factor to impaired postoperative function.

Fibrosis, often extensive, may accompany myocardial hypertrophy in valvular heart disease, and it is likely that myocardial hypertrophy is less reversible in those patients with considerable preoperative fibrosis. Moderately or severely increased interstitial fibrous tissue (grade III or IV) (Fig. 2) and loss of myofibrillar components from the massively hypertrophied myocardial cells correlated with postoperative ventricular dilatation and impaired function (Tables 1 and 2). Most of the patients reinvestigated from group B had severe postoperative hypertrophy (mean 32·5 μm) and persistently increased fibrous collagen tissue. The three patients who died from congestive failure during follow-up were in this group B. Similar correlation between postoperative symptoms of cardiac failure and preoperative fibrosis has recently been reported.[17]

Histochemical studies on the tissues obtained before and after surgery from patients with postoperative cardiac dilatation (group B) showed abnormalities in the levels of certain enzyme markers (Tables 1 and 2). Eleven out of these 16 patients had reduced levels of myofibril associated Ca^{++} dependent ATPase before valve replacement, and this abnormality was documented in six out of the eight patients restudied from this group. It is likely that this was associated with grossly impaired ventricular function[18]; the defective utilisation of high energy phosphates by the myofibrils and decreased metabolic substrates such as glycogen could also have contributed to further depression of the contractile function. Chronic mechanical overloading in rats may cause an isoenzymic shift in the composition of cardiac myosin[19] which could also partially account for the lower ATPase activity and decreased contractility.

The decreased level of the mitochondrial enzyme succinate dehydrogenase in the biopsies from patients in group B (Tables 1 and 2) is of interest, suggesting perhaps an irreversible abnormality in the properties or function of mitochondria.[20] Further work on the biochemical basis of physiological and pathological adaptations will undoubtedly elucidate the relevance of these histochemical observations.

A normal preoperative biopsy was sensitive in identifying patients with an eventual successful outcome after valve replacement; the predictive value of this test was 89%. Five patients, however, with normal preoperative histological studies deteriorated postoperatively, with echocardiographic evidence of persistent dilatation and hypertrophy. As prosthetic valve function was normal in these five patients, it can be speculated that operative factors such as myocardial ischaemia during the operation could have adversely affected cardiac haemodynamics. Histochemical changes resulting from cardiopulmonary bypass have been documented; methods of myocardial protection during this type of surgery have been evaluated using histochemical variables.[21]

An abnormal biopsy had a lower sensitivity in predicting an unsuccessful outcome after valve replacement. Among 18 patients with abnormal myocardial histology or histochemistry, 11 (61%) developed persistent dilatation and hypertrophy after surgery, and three of these 11 patients died from cardiac failure during the follow-up period. The fact that one-third of the patients with abnormal biopsies improved clinically and echocardiographically, however, remains unexplained and reduces the prognostic accuracy of this method.

Because of the possible considerable topographic variation of the structured composition of the myocardium in chronic aortic regurgitation, we also compared data from the small bioptome biopsies with those obtained from the larger operative specimen in 15 patients before valve replacement. A good correlation was present, and these data confirm our recent observation[22] that, provided a minimum of four biopsies are obtained, small tissue samples are accurate in evaluating morphology and can therefore be used to predict prognosis.

IMPLICATIONS OF STUDY

The serial application of electrocardiography and echocardiography to patients undergoing valve replacement for chronic severe aortic regurgitation documented regression of hypertrophy and chamber size within 12 months of surgery in all cases experiencing haemodynamic improvement. Those patients who had persistently increased patterns of myocardial hypertrophy and abnormal end-diastolic dimensions in the presence of normal prosthetic (homograft) function usually had persistent, irreversibly depressed myocardial function postoperatively (Table 3). Preoperative non-invasive and angiographic characteristics could not predict ventricular function after operation. Thus we could not define precisely what level of depressed ventricular performance or what degree of dilatation and myocardial hypertrophy constitutes an irreversible state from these data. Though operative factors such as myocardial protection during cardiopulmonary bypass undoubtedly influence postoperative cardiac performance, preoperative histological and histochemical data were useful in delineating irreversible morphological and functional changes contributing to a

Table 3 *Pre- and postoperative pointers to irreversible morphological changes contributing to a depressed cardiac function after surgery for chronic aortic regurgitation*

(1) *Preoperative ventricular biopsy data*		
		Massively increased myocardial fibre diameter (>30 μm)
		Grossly abnormal fibrous content
		Reduced levels of histochemical markers (ATPase, succinate dehydrogenase, glycogen)
(2) *Postoperative data*		
(A) Non-invasive		*Electrocardiography*
	(i)	Persistently increased left ventricular voltages
		or
		Progressive conduction abnormalities 6 to 12 months after operation
		Echocardiography
	(ii)	Abnormal end-diastolic dimension six months after surgery
		Abnormal estimates of muscle mass 12 months after surgery
(B) Invasive		*Angiography*
		Impaired systolic function and regional wall motion despite satisfactory valve function and normal coronary anatomy

depressed cardiac function. These data may therefore be of prognostic importance.

Conclusion

Because irreversible myocardial depression may be present before the development of significant symptoms, aortic valve replacement may sometimes be recommended in patients with aortic regurgitation and minimal symptoms. Our echocardiographic and angiographic data could not define the type and degree of ventricular dysfunction which was irreversible. Preoperative ventricular biopsies suggest that extensive morphological changes contribute to depressed postoperative function, and these histological data appear to be of prognostic significance.

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Case reports

Two dimensional echocardiographic diagnosis of partial papillary muscle rupture

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SUMMARY Two dimensional echocardiography showed partial rupture of the trunk of the posteromedial papillary muscle after acute inferior myocardial infarction. The findings in this case suggest that partial rupture may be a harbinger of complete rupture.

By virtue of its ability to visualise noninvasively detailed anatomy of cardiac structures in real-time format, two dimensional echocardiography is ideally suited to diagnose mechanical (structural) complications of acute myocardial infarction. Structural disruptions after acute myocardial infarction are uncommon but are potentially correctable with timely diagnosis and treatment.[1 2] We describe a patient with acute partial papillary muscle rupture, complicating acute myocardial infarction, diagnosed by two dimensional echocardiography.

Case report

A 67 year old white man was transferred to the Mayo Clinic for evaluation of cardiogenic shock. He had a history of stable angina but no hypertension or previous myocardial infarction. Two weeks before transfer, the patient sustained an acute inferior myocardial infarction, was admitted to hospital, and was found to be in shock, with pulmonary oedema. Despite initial improvement with medical treatment, he subsequently became hypotensive again and was transferred for further evaluation.

On physical examination, the patient was in respiratory distress. The blood pressure was 100/60 mmHg and the pulse 100/min. The jugular venous pressure was raised. Bibasilar râles were noted. The left ventricular impulse, located in the anterior axillary line, was widened and hyperdynamic. No thrill was palpable. A grade 4/6 pansystolic apical murmur and a third sound were present. The remainder of the physical examination was normal.

An electrocardiogram showed sinus rhythm and changes consistent with a recent inferior wall myocardial infarction. The chest *x*-ray film showed cardiac enlargement with pulmonary venous congestion. Bedside assessment of the haemodynamic data (Swan-Ganz catheter) is shown in the Table.

Two dimensional echocardiography showed that the left ventricle was moderately dilated with depressed function. There was extensive and severe inferior wall hypokinesis, with involvement of the inferior septum and lateral walls as well, consistent with a large inferolateral wall infarction. The anterior ventricular septum was hyperdynamic. A partial rupture of the trunk of the posteromedial papillary muscle was seen (Fig), with normal coaptation of the mitral leaflets.

Using afterload reduction treatment and positive inotropic agents, the patient's condition remained stable. On the seventh hospital day, the patient suddenly became hypotensive and dyspnoeic, with an increase in the size of the "V" wave on the wedge tracing. This rapid deterioration was thought to be the result of further rupture of the posteromedial papillary muscle. A percutaneous intra-aortic balloon was inserted, and at operation the entire posteromedial papillary muscle was described as necrotic and ruptured. The mitral valve was excised and replaced with an Ionescu-Shiley valve. The patient's condition deteriorated after being taken off the bypass pump, and he died.

Table *Haemodynamic data (Swan-Ganz catheter) in patient with partial papillary muscle rupture*

Variable	*Value*
Right atrial pressure (mmHg)	17
Right ventricle pressure (mmHg)	66/22
Pulmonary trunk pressure (mmHg)	65/38
Pulmonary capillary wedge pressure (mmHg)	21 40 ("V" wave)
Cardiac index (l/min per m^2)	1·9
No O_2 step-up	

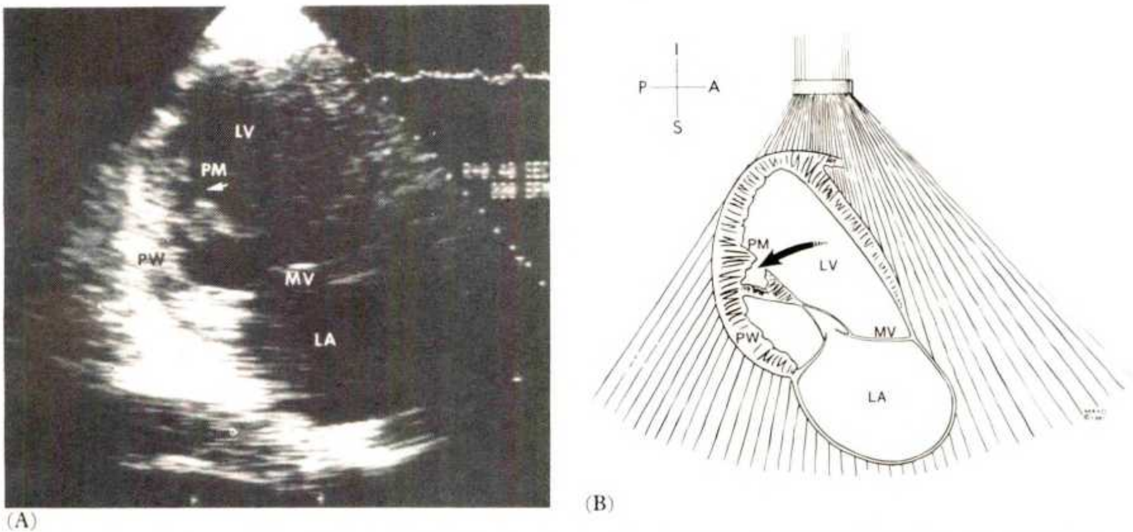

Fig. *(A) Two dimensional echocardiogram. Apical view showing partial rupture (arrow) of posteromedial papillary muscle (PM). (B) Schematic diagram depicting structures seen in (A). PW, posterior wall; LV, left ventricle; LA, left atrium; MV, mitral valve.*

Discussion

Rupture of a papillary muscle is a rare complication of acute myocardial infarction, being found in 0·9% of fatal myocardial infarctions at necropsy.[3] Rupture of the posteromedial papillary muscle is 250% more frequent than rupture of the anterolateral muscle, because of the former's single blood supply from the posterior descending coronary artery.[4] Rupture usually occurs during the second or third day after infarction but may occur later, with immediate death in 33% and death within 24 hours in 50% of patients.[3] Because papillary muscle rupture is usually associated with small areas of necrosis and sparing of the myocardium surrounding the annulus,[5] early surgical intervention has been suggested to improve an otherwise poor prognosis.[6,7]

Recent reports have described the usefulness of two dimensional echocardiography in the diagnosis of complete rupture of the papillary muscle head(s).[8,9] In our case, the echocardiographic observations suggested that the initial problem was that of partial rupture of the trunk of the posterior papillary muscle. The subsequent sudden clinical deterioration with worsening of mitral regurgitation that occurred several days later represented delayed complete rupture of the papillary muscle (as found at operation).

This observation supports the idea that complete (total) rupture of the papillary muscle may sometimes occur in stages, and that two dimensional echocardiography can be used successfully for diagnosis of partial (early) rupture. Since partial rupture is probably a harbinger of complete rupture of a papillary muscle, visualisation of partial rupture of the trunk by two dimensional echocardiography may help identify high risk patients and may constitute an indication for earlier surgical intervention.

This case further extends the usefulness of two dimensional echocardiography in elucidating the cause of sudden haemodynamic deterioration after acute myocardial infarction.

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Br Heart J 1982; **48**: 601–3

Anomalous low insertion of right superior vena cava

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SUMMARY A 7 year old boy with complex congenital heart disease had a distinctive chest radiograph, and venous angiography showed anomalous low insertion of the right superior vena cava.

Among patients with congenital heart disease, anomalies of the right superior vena cava are relatively uncommon.[1-3] The usual anomalies are congenital absence, anomalous drainage of the right superior vena cava into the left atrium as an isolated anomaly, congenital saccular aneurysm, and idiopathic dilatation of the right superior vena cava.[4 5]

We report a rare anomaly of the right superior vena cava in a 7 year old boy with complex congenital heart disease who presented to The Hospital for Sick Children, Toronto.[6]

Case report

This child presented at 5 weeks of age with mild cyanosis and congestive heart failure. The electrocardiogram showed so-called coronary sinus rhythm with a normal PR interval and negative P waves in leads II, III, and aVF. The frontal qRS axis was +80° and biventricular hypertrophy was evident. The chest *x*-ray film indicated a widened mediastinum, cardiomegaly, and pulmonary plethora. The heart was left sided and there was situs solitus.

On cardiac catheterisation, the systemic saturation was 91% and the pulmonary artery pressure was at systemic level. Angiography showed a single left ventricle, an outlet chamber, and concordant ventriculoarterial connections. The atrial situs was normal with right sided superior and inferior vena cavae and a left superior vena cava connected to the coronary sinus. Antifailure treatment was given, but because of refractory congestive heart failure the child underwent pulmonary artery banding and ligation of the left superior vena cava.

Subsequent growth and development were excellent. Follow-up catheterisation at 7 years of age showed that systemic arterial oxygen saturation was 86%. The pulmonary arterial pressure distal to the band was 13/8 mmHg (mean 10 mmHg) and the peak systolic right ventricular pressure was equal to systemic pressure. Ventricular angiography confirmed the anatomy and showed the pulmonary artery band. Because the chest *x*-ray was unusual (Fig. 1), contrast material was injected in the right superior vena cava (Fig. 2). This showed anomalous low insertion of the right superior vena cava to the morphological right atrium, with separate atrial insertions of the superior and inferior vena cava.

Discussion

In 1975, Takanashi and colleagues[7] reported anomalous high insertion of the inferior vena cava in a patient with a common atrium. They suggested that this venous anomaly originated from developmental failure of the sinoatrial fold and subsequent incomplete differentiation of the sinus venosus and its tributaries. In our case, the mechanism appears to be developmental failure of the right sinoatrial fold and incomplete absorption of the right anterior cardinal vein into the right limb of the sinus venosus.

The diagnosis of this most uncommon anomaly could have been suspected from the plain chest *x*-ray. The vertical density to the right of the mediastinum was not typical of anomalous pulmonary venous drainage or the "scimitar" syndrome. Dupuis and colleagues[6] showed a very similar angiogram and described one patient in whom the right superior vena cava also assumed an extramediastinal course.

Absence of the brachiocephalic vein was suggested as the cause of an extramediastinal superior vena cava.[6] Our experience suggests otherwise. In assessing systemic venous connections in hundreds of patients with congenital heart disease we have identified many cases with normal visceral and atrial situs and bilateral superior vena cavae with the left superior vena cava connecting to the coronary sinus without an intervening left brachiocephalic vein. Only the patient we are reporting now had such an abnormal plain chest *x*-ray or angiogram.

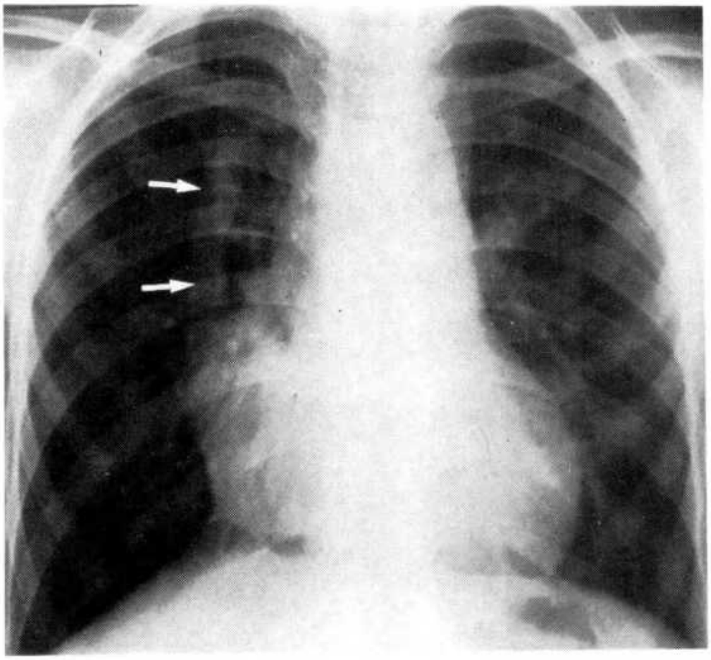
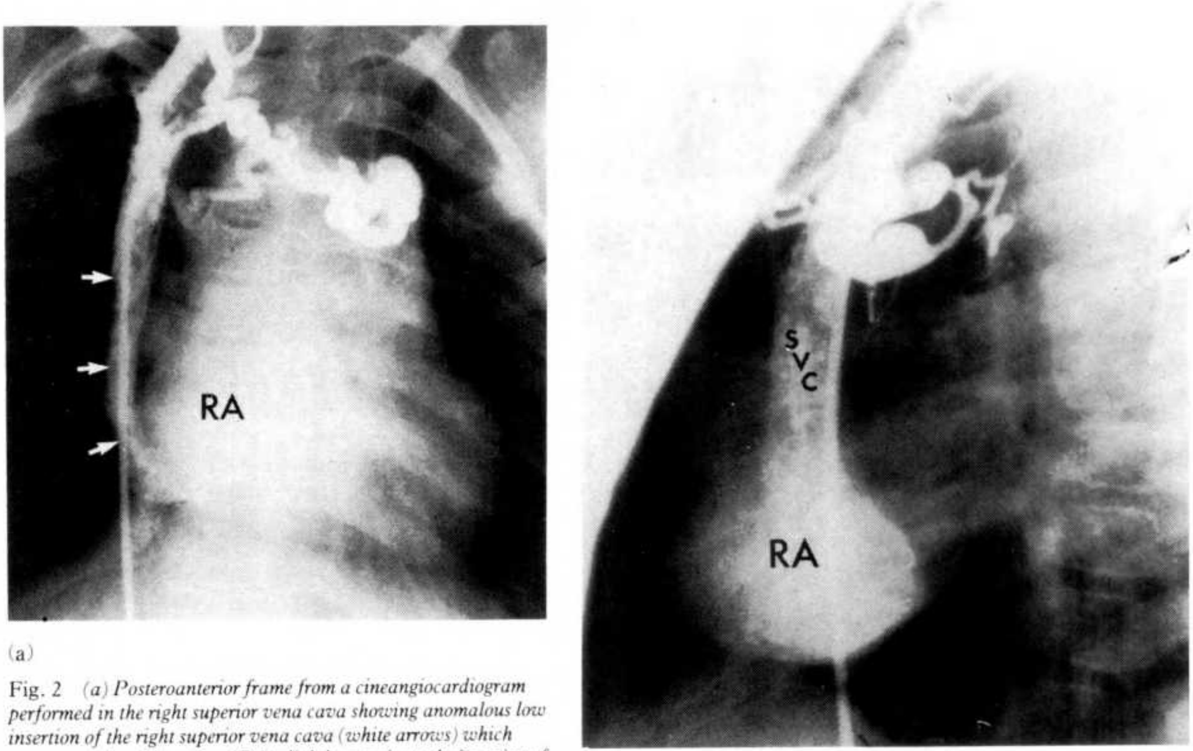


Fig. 1 *Posteroanterior chest x-ray showing a vertically orientated linear area of increased density in the right thorax (white arrow) surrounded by lung. The heart is mildly enlarged and centrally positioned in the chest; the pulmonary band is in place.*



(a)

(b)

Fig. 2 *(a) Posteroanterior frame from a cineangiocardiogram performed in the right superior vena cava showing anomalous low insertion of the right superior vena cava (white arrows) which connects to the right atrium (RA) slightly superior to the insertion of the right sided inferior vena cava. (b) Lateral of this injection.*

It is not surprising that our patient showed so-called coronary sinus rhythm on the surface electrocardiogram.[8 9] Though this rhythm is rarely seen in normal subjects, it is common among patients with intrinsic abnormalities of the sinus venosus, for example those with sinus venosus atrial septal defect, or the polysplenia syndrome with azygos continuation of the inferior vena cava. This rhythm implies that the sinoatrial node is abnormal and the atrial pacemaker is ectopic. Electrophysiological studies indicate that the abnormal P wave axis originates in the inferior left atrium or lower right atrium (including the orifice of the coronary sinus).

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Requests for reprints to Dr Robert M Freedom, Department of Cardiology, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

Correspondence

Br Heart J 1982; 48: 604

Immunological probes in cardiovascular disease

Sir,

Dr Haber's recent paper (*Br Heart J* 1982; **47**: 1–10) describes the use of Fab (digoxin-specific Fab fragments of sheep IgG/Wellcome) in the treatment of digoxin toxicity. We have used the drug in 13 patients who we felt would benefit from the rapid reversal of the effects of digoxin. Clinical and electrocardiographic improvement occurred within four hours in all toxic patients treated, with the exception of a neonate who was asystolic for 10 minutes before Fab was given. There were no overt immunological or haemodynamic side effects.

We feel that attention should be drawn to the results (Table) obtained with various radioimmunoassays before and after Fab treatment. The assays gave acceptably similar results for samples before Fab, but we found a wide variation in values after treatment. Interpretation of the data from all three assays is difficult, but method B, involving a charcoal separation, probably reflects digoxin in excess of the binding capacity of Fab, while method C, which employs a solid phase antibody, probably indicates the excess of digoxin binding sites. The polyethylene glycol (PEG) assay results are the most difficult to interpret as they give an unreliable measure of the lowering of digoxin levels as a result of variable Fab interference in the assay.

Table *Plasma digoxin levels (μg/l)*

	Assay method		
	A	*B*	*C*
Before Fab	4·5	5·1	4·6
60 minutes after Fab	1·5	ND	25

ND, not detected.
A: In-house, PEG.
B: Becton-Dickinson Immunodiagnostics Kit.
C: Corning Medical and Scientific Kit.

We suggest that a charcoal based assay may give the simplest, most readily available indication of the circulating bioavailable digoxin, avoiding lengthy equilibrium dialysis procedures. Studies are in progress to validate the use of simple assay techniques to measure the concentration of bound and unbound digoxin and total Fab binding capacity, and to characterise Fab pharmacokinetics in man.

K Jennings,
P C Adams,
I Gibb,
A J Parnham,
Department of Cardiology,
Freeman Hospital,
Newcastle upon Tyne NE7 7DN.

This letter was shown to Dr Haber who replies as follows:

Sir,

The question raised by Jennings and his colleagues is a difficult one to resolve. None of the methods that they have used to determine free digoxin concentration is entirely reliable. As they correctly point out, assay methods based on an immobilised antibody yield false results because all the labelled digoxin is bound to excess Fab from the patient's plasma. Any assay method based on precipitation of antibody will give uncertain results, because the conditions for precipitation of Fab and antibody differ and are dependent on the method chosen. The charcoal method for absorbing free digoxin is likely to be more reliable, but only if the affinity of the Fab used in therapy is similar or higher than the affinity of the assay antibody. If the Fab is of significantly lower affinity, then there will be transfer of labelled digoxin from Fab to charcoal, resulting in falsely raised free digoxin concentrations.[1 2] The only entirely reliable method is equilibrium dialysis, though this is admittedly tedious, time consuming, and not really applicable to the routine clinical laboratory.

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Edgar Haber,
Cardiac Unit of the Medical Services,
Massachusetts General Hospital,
Boston, Mass., USA.

Correspondence

Br Heart J 1982; **48**: 605

Echocardiographic dimensions

Sir,

The terms used to describe echocardiographic displays give food for thought. M-mode display is usually distinguished from the more recently developed formats which more readily show anatomical structure. The latter tend to be described as either "two dimensional" or "cross-sectional". Neither is perfect to distinguish this display from M-mode, because the M-mode technique also displays cross-sectional anatomy. It does so in at least the two dimensions of length and breadth, the breadth representing the dimension of time. What is certain is that it is incorrect, as Veyrat and her colleagues do in the June issue,[1] to describe M-mode echocardiography as "one dimensional". I am told that it is not possible for anything to exist in only one dimension. If one uses the term "two dimensional" to describe the more obviously cross-sectional format, there is the immediate temptation to contrast the M-mode technique as "one dimensional". Might I suggest it would be good general editorial policy to avoid references to dimension and to distinguish the different displays as "M-mode" and "cross-sectional", respectively.

R H Anderson,
Cardiothoracic Institute,
Fulham Road,
London SW3.

Reference

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Notices

Br Heart J 1982; 48: 606

European Society of Cardiology working group on "Thrombosis and platelets"

This meeting, to be held in Bordeaux, France, on 7 to 9 April 1983, will be entitled "Anti-aggregative agents: mode of action and clinical evaluation. Progress report and new developments". Inquiries to Professor H Bricaud, CHU de Bordeaux, Haut Lévêgne, 33604 Pessac, France.

International Congress on Electrocardiology

The 10th International Congress on Electrocardiology (24th International Symposium on Vectorcardiography) will be held on 16 to 19 August 1983 in Bratislava, Czechoslovakia. For further information contact: Dr I Ruttkay-Nedecký, 81371 Bratislava, Siekiewiczova 1, Czechoslovakia.

Subacute bacterial endocarditis

A survey is currently being carried out by the British Cardiac Society and the Medical Services Study Group of the Royal College of Physicians. Though improvement of dental prophylaxis is one objective, the survey is already yielding other valuable information. It is hoped that proformas will be received in respect of a high proportion of patients with subacute bacterial endocarditis in the British Isles seen during 1981 and 1982 and readers are asked to arrange for them to be submitted in respect of any cases that come to their notice. Proformas can be obtained from Sir Cyril Clarke, Medical Services Study Group, King's Fund Centre, 126 Albert Street, London NW1 7NF (tel. 01-267 6111, ext. 263) to whom they should be returned.

British Cardiac Society

The Annual General Meeting for 1983 will take place in Bristol on 12 and 13 April, and the closing date for abstracts will be 4 January 1983.

The Autumn Meeting will be held at Wembley on 21 and 22 November 1983, and the closing date for abstracts will be 28 July 1983.

AUTHOR INDEX

1982, Volume 48

Abe H *see* Matsumoto M *et al*
Abinader E G (& Shahar J) Exercise testing in mitral valve prolapse before and after beta blockade 130
Ackroyd S *see* deGiovanni J V *et al*
Adams P C *see* Jennings K *et al*
Adgey A A J *see* Pringle T H *et al*
Ahuja R C *see* Silke B *et al*
Altman D G *see* Mann S *et al*
Alvares R F (& Goodwin J F) Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs 204
Amery A *see* Vanhees L *et al*
Amlie J P *see* Landmark K *et al*
Andersen K (& Vik-Mo H) Role of the Frank-Starling mechanism during maximal semisupine exercise after oral atenolol 149
Anderson R H Echocardiographic dimensions: correspondence 605
– Hang-out time of pulmonary valve in d-transposition of great arteries; correspondence 302
– *see also* Deanfield J E *et al*
    Huhta J C *et al*
    Restivo A *et al*
    Smallhorn J F *et al*
Anderson V *see* Brown A K *et al*
Anson R Canepa- *see* Canepa-Anson R
Atkinson L *see* Richardson P J *et al*

Bain H H *see* Morrell P *et al*
Ballester M *see* Donaldson R M *et al*
Bannister R *see* Mann S *et al*
Bardos P *see* Schweizer P *et al*
Baron M (& Skrinskas G, Hyland R, Urowitz M B) Effects of prostaglandin E_1 and other vasodilator agents in pulmonary hypertension of scleroderma: correspondence 304
Bauernfeind R A (& Strasberg B, Rosen K M) Slowing of paroxysmal tachycardia with loss of functional bundle-branch block: case report 75
Bayliss J (& Norell M, Canepa-Anson R, Reuben S, Poole-Wilson P A, Sutton G C) Interaction between inotropism and vasodilatation in heart failure 93 *P*
Beach C (& Kenmure A C F, Short D) Electrocardiogram of pure left ventricular hypertrophy and its differentiation from lateral ischaemia: correspondence 85
Beeching N J *see* Voulgari F *et al*
Beil U *see* Mathey D G *et al*
Bell J A (& Thomas J M, Isaacson J R, Snell N J C, Holt D W) A trial of prophylactic mexiletine in home coronary care 285
Benmimoun E G (& Friedli B, Rutishauser W, Faidutti B) Mitral valve replacement in children. Comparative study of pre- and postoperative haemodynamics and left ventricular function 117
Bennett J G *see* Donaldson R M *et al*
Bergman G *see* Kenny J *et al*
Bernuth G von *see* von Bernuth G
Bexton R S (& Hellestrand K J, Cory-Pearce R, Spurrell R A J, English T A H, Camm A J) Direct electrophysiological effects of disopyramide phosphate–evaluated in denervated human heart 87 *P*
– *see also* Cory-Pearce R *et al*
    Hellestrand K J *et al*
    Nathan A W *et al*
Bini R M *see* Milanesi O *et al*
Bjarnason I (& Hardarson T, Jonsson S) Cardiac arrhythmias in hypertrophic cardiomyopathy 198
Bleifeld W *see* Matsumoto M *et al*
Bonvicini M (& Piovaccari G, Picchio F M) Severe subpulmonary obstruction caused by an aneurysmal tissue tag complicating an infundibular perimembranous ventricular septal defect: case report 189
Boyle R *see* Elamin M S *et al*
British Cardiac Society, 61st Annual General Meeting, Nottingham, April 1982, proceedings, 87
Brooksby I A B *see* Williams K N *et al*
Brown A K (& Anderson V, Gillgren C L) Echocardiographic diagnosis of isolated pulmonary valve endocarditis: correspondence 307
Bullock R E (& Hall R J C) Left ventricular function and mitral valve opening in massive pulmonary embolism: case report 413

Caccavano M *see* Zema M J and Caccavano M
Cameron H *see* Restivo A *et al*
Camm A J *see* Bexton R S *et al*
    Cory-Pearce R *et al*
    Hellestrand K J *et al*
    Nathan A W *et al*
Canepa-Anson R *see* Bayliss J *et al*
    Ilsley C *et al*
Carboni G P *see* Lahiri A *et al*
Carmichael D J *see* Mackintosh A F *et al*
Castellanos A (& Ferreiro J, Pefkaros K, Rozanski J J, Moleiro F, Myerburg R J) Effects of lignocaine on bidirectional tachycardia and on digitalis-induced atrial tachycardia with block 27
Char G *see* Dianzumba S B and Char G
Cheng T O Mitral valve prolapse and coronary artery spasm: correspondence 301
Cleland J *see* Pringle T H *et al*
Clitsakis D *see* Ilsley C *et al*
Cochrane T *see* Cory-Pearce R *et al*
Coleman E N *see* Reid J M *et al*
Coltart D T *see* Wilmshurst P T *et al*
Cory-Pearce R (& Bexton R S, Cochrane T, Camm A J, English T A H) Increased atrial pacing threshold in heart transplant rejection 89 *P*
– *see also* Bexton R S *et al*
    Mackintosh A F *et al*
Coulibaly A O *see* Metras D *et al*
Crawley J W *see* Lahiri A *et al*
Cummins P *see* Voulgari F *et al*
Curry P V L *see* Davies D W *et al*

D'Alnoncourt C N (& Zierhut W, Lüderitz B) "Torsade de pointes" tachycardia. Re-entry or focal activity? 213
Daly K (& Richardson P J, Olsen E G J, Pattison J, Jackson G, Jewitt D E) Immunosuppressive therapy in acute inflammatory myocarditis 94 *P*
– *see also* Kenny J *et al*

Dancy M (& Leech G, Leatham A) Significance of complete right bundle-branch block when an isolated finding. An echocardiographic study 217
Davies D W (& Holt P M, Curry P V L) Relation between episodes of reversible cardiac ischaemia and arrhythmias 90 *P*
Davies E R *see* Walker P R *et al*
Davies J (& Gibson D G, Foale R, Heer K, Spry C J F, Oakley C M, Goodwin J F) Echocardiographic features of eosinophilic endomyocardial disease 434
Davignon A *see* Fouron J C *et al*
Deanfield J *see* Fox K M *et al*
Deanfield J E (& Sugrue D, McKenna W J, Lavender P, Graham G R, Hallidie-Smith K) Ventricular arrhythmia in tetralogy of Fallot: influence of age, haemodynamic factors, and surgery 88 *P*
– (& Tommasini G, Anderson R H, Macartney F J) Tricuspid atresia: analysis of coronary artery distribution and ventricular morphology 485
De Giovanni J V (& Ackroyd S, Green S H, Silove E D) Cardiomyopathy in Friedreich's ataxia 92 *P*
De Groot A C Gittenberger- *see* Gittenberger-de Groot A C
De Leval M *see* Huhta J C *et al*
McKay R *et al*
Shore D F *et al*
Smallhorn J F *et al*
Der Hauwaert L G Van *see* Van der Hauwaert L G
Deverall P B *see* Reidy J F *et al*
Dianzumba S B (& Char G) Large calcified right atrial myxoma in a newborn. Rare cause of neonatal death: case report 177
Dickinson D F (& Parimelazhagan K M, Tweedie M C K, West C R, Piccoli G P, Musumeci F, Hamilton D I) Total anomalous pulmonary venous connection. Repair using deep hypothermia and circulatory arrest in 44 consecutive infants 249
Dillon J C Measurement of pulmonary artery pressure in cyanotic heart disease using selective coronary artery cannulation techniques: case report 504
Doesburg N Van *see* van Doesburg N
Doig W *see* Reid J M *et al*
Donaldson R M (& Ballester M, Rickards A F) Rupture of a papillary muscle of the triscupid valve. Echocardiographic diagnosis: case report 291
– (& Florio R, Rickards A F, Bennett J G, Yacoub M, Ross D N, Olsen E) Irreversible morphological changes contributing to depressed cardiac function after surgery for chronic aortic regurgitation 589
– (& Olsen E, Florio R, Emanuel R, Rickards A F, Bennett J G, Ross D N) Changes in left ventricular mass, volume, and function after surgery for chronic aortic regurgitation 92 *P*
– (& Rickards A F) Evaluation of drug-induced changes in myocardial repolarisation using the paced evoked response 381
Dumoulin M *see* Van der Hauwaert L G *et al*

Edwards C W *see* Lowry P J *et al*
Effert S *see* Schweizer P *et al*
Elamin M S (& Boyle R, Kardash M M, Smith D R, Stoker J B, Whitaker W, Mary D A S G, Linden R J) Accurate detection of coronary heart disease by new exercise test 311
Eldar M (& Motro M, Rath S, Schy N, Neufeld H N) Systolic closure of aortic valve in patients with prosthetic mitral valves 48
Ell P J *see* Walton S *et al*
Ellison R C *see* Hofman A *et al*
Emanuel R *see* Donaldson R M *et al*
Engel S *see* Schlüter M *et al*
England D *see* Fox K M *et al*
English T A H *see* Bexton R S *et al*
Cory-Pearce R *et al*
Mackintosh A F *et al*
Erbel R *see* Schweizer P *et al*
Erikssen J *see* Thaulow E *et al*
Errington J *see* Henderson A & Errington J
Espiner E A *see* Ikram H *et al*
Evemy K (& Sutherland G, Hunter S) Demonstration of defects of interventricular septum in adults by two dimensional echocardiography 95 *P*
– *see also* Jennings K *et al*
Fagard R *see* Vanhees L *et al*
Faidutti B *see* Benmimoun E G *et al*
Falk E Coronary artery narrowing without irreversible myocardial damage or development of collaterals. Assessment of "critical" stenosis in a human model 265
Ferreiro J *see* Castellanos A *et al*
Fiddler G I *see* Gerlis L M *et al*
Firth B G *see* Rehr R B *et al*
Fitzgerald D J (& O'Callaghan W G, McQuaid R, O'Malley K, O'Brien E) Accuracy and reliability of two indirect ambulatory blood pressure recorders: Remler M2000 and Cardiodyne Sphygmolog 572
Florio R *see* Donaldson R M *et al*
Foale R *see* Davies J *et al*
Forfar J C (& Muir A L, Toft A D) Left ventricular function in hypothyroidism. Responses to exercise and beta adrenoceptor blockade 278
Fortuin N J *see* Traill T A & Fortuin N J
Fouron J C (& van Doesburg N, Davignon A) Hang-out time of pulmonary valve in d-transposition of great arteries: correspondence 302
Fox K M Exercise heart rate/ST segment relation. Perfect predictor of coronary disease? editorial 309
– (& Deanfield J, Ribero P, England D, Wright C) Projection of ST segment changes on to the front of the chest. Practical implications for exercise testing and ambulatory monitoring 555
Frand M *see* Laufer J *et al*
Freedom R M (& Schaffer M S, Rowe R D) Anomalous low insertion of right superior vena cava: case report 601
Friedli B *see* Benmimoun E G *et al*
Fujita T *see* Miyatake K *et al*

Gaba F E *see* George B O *et al*
Gardecki T I M *see* Voulgari F *et al*
Gelman J S (& Saltups A) Precordial ST segment depression in patients with inferior myocardial infarction: clinical implications 560
George B O (& Gaba F E, Talabi A I) M-mode echocardiographic features of endomyocardial fibrosis 222
Gerlis L M (& Partridge J B, Fiddler G I) Anomalous connection of left atrial appendage with persistent left superior vena cava: case report 73
Gibb I *see* Jennings K *et al*
Gibson D *see* Oldershaw P J *et al*
Gibson D G *see* Davies J *et al*
Sutton M G St J *et al*
Giessen W J v d *see* Stoel I *et al*
Gillgren C L *see* Brown A K *et al*
Giovanni J V de *see* de Giovanni J V
Gittenberger-de Groot A C *see* Wenink A C G & Gittenberger-de Groot A C
Goiti J J (& Smith G H) Coronary artery surgery using inverted internal mammary artery: case report 81
Goodwin J F The frontiers of cardiomyopathy 1
– *see also* Alvares R F & Goodwin J F
Davies J *et al*
Gowers J *see* Veale D *et al*
Graham G R *see* Deanfield J E *et al*
Green S H *see* de Giovanni J V *et al*
Greenberg G (& Imeson J D, Meade T W) Endogenous progesterone and blood pressure 92 *P*
Groot A C Gittenberger-de *see* Gittenberger-de Groot A C

Haber E Immunological probes in cardiovascular disease: correspondence 604

Hagworth S G Total anomalous pulmonary venous return. Prenatal damage to pulmonary vascular bed and extrapulmonary veins 513

Hall R J C *see* Bullock R E & Hall R J C

Hallidie-Smith K *see* Deanfield J E *et al*

Hamilton D I *see* Dickinson D F *et al*

Handa S *see* Yamazaki H *et al*

Hanrath P *see* Matsumoto M *et al*
    Schlüter M *et al*

Hardarson T *see* Bjarnason I *et al*

Hauge S Nitter- *see* Nitter-Hauge S *et al*

Hauwaert L G van der *see* Van der Hauwaert L G

Heer K *see* Davies J *et al*

Hellestrand K J (& Bexton R S, Nathan A W, Spurrell R A J, Camm A J) Acute electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness in man 140

– *see also* Bexton R S *et al*
    Nathan A W *et al*

Henderson A (& Errington J) Sudden versus gradual withdrawal of sotalol in ambulant patients with ischaemic heart disease 552

Hickey A J (& Wolfers J, Wilcken D E L) Reliability and clinical relevance of detection of vegetations by echocardiography in bacterial endocarditis: correspondence 83

Hirose H *see* Matsumoto M *et al*

Ho S Y *see* Restivo A *et al*

Hofman A (& Ellison R C, Newburger J, Miettinen O S) Blood pressure and haemodynamics in teenagers 377

Hofstetter R (& Mayr A, Von Bernuth G) Computer analysis of cardiac contractility variables obtained by M-mode echocardiography in normal newborns 525

Holt D W *see* Bell J A *et al*

Holt P M *see* Davies D W *et al*

Hoor F ten *see* ten Hoor F

Houseago S *see* Williams K N *et al*

Huckell V F Mitral valve prolapse and coronary artery spasm: correspondence 301

Hugenholtz P G *see* Stoel I *et al*

Huhta J C (& Smallhorn J F, Macartney F J) Two dimensional echocardiographic diagnosis of situs 97

– – – Anderson R H, de Leval M) Cross-sectional echocardiographic diagnosis of systemic venous return 388

– *see also* Smallhorn J F *et al*

Huhtra J *see* Smallhorn J F *et al*

Hull F T L *see* Ikram H *et al*

Hunter S *see* Evemy K *et al*
    Morrell P *et al*

Hyland R *see* Baron M *et al*

Ikram H Effects of prostaglandin E$_1$ and other vasodilator agents in pulmonary hypertension of scleroderma: correspondence 304

– (& Maslowski A H, Nicholls M G, Espiner E A, Hull F T L) Haemodynamic and hormonal effects of captopril in primary pulmonary hypertension 541

Ilsley C (& Canepa-Anson R, Westgate C, Webb S, Rickards A, Poole-Wilson P) Influence of R wave analysis upon diagnostic accuracy of exercise testing in women 161

– (& Stockley A, Clitsakis D, Layton C) Normal coronary arteriogram. An avoidable test? 580

Imeson J D *see* Greenberg G *et al*

Imm S *see* Schweizer P *et al*

Inoue T *see* Yamazaki H *et al*

Isaacson J R *see* Bell J A *et al*

Jackson G *see* Daly K *et al*
    Kenny J *et al*

Jarritt P H *see* Walton S *et al*

Jenkins B S *see* Wilmshurst P T *et al*

Jennings K (& Adams P C, Gibb I, Parnham A J) Immunological probes in cardiovascular disease: correspondence 604

– (& Evemy K, Reid D S, Julian D G) Reciprocal ST depression in myocardial infarction: relation to exercise-induced ST depression 90 *P*

Jewitt D E *see* Daly K *et al*
    Kenny J *et al*
    Richardson P J *et al*

Jonsson S *see* Bjarnason I *et al*

Joy M (& Pollard C M, Nunan T O) Diurnal variation in exercise responses in angina pectoris 156

Julian D G *see* Jennings K *et al*

Kardash M M *see* Elamin M S *et al*

Karliner J *see* Watkins J *et al*

Kawazoe K *see* Miyatake K *et al*

Keenan D J M (& Morton P, O'Kane H O) Right atrial myxoma and pulmonary embolism. Rational basis for investigation and treatment: case report 510

Kenmure A C F *see* Beach C *et al*

Kenny J (& Daly K, Bergman G, Kerkez S, Jackson G, Jewitt D E) Haemodynamic and metabolic effects of diltiazem, a new calcium antagonist, compared with nifedipine in patients with coronary artery disease 89 *P*

Kekwick C A *see* Veale D *et al*

Kerkez S *see* Kenny J *et al*

Khan M M *see* Pringle T H *et al*

Kinoshita N *see* Miyatake K *et al*

Kishi H *see* Watanabe Y and Kishi H

Kitchin A H *see* Marquis R M *et al*

Klöppel G *see* Mathey D G *et al*

Kondo M *see* Yamazaki H *et al*

Krebs W *see* Schweizer P *et al*

Kremer P *see* Matsumoto M *et al*
    Schlüter M *et al*

Krikler D M *see* Rowland E *et al*

Kubo A *see* Yamazaki H *et al*

Kuck K-H *see* Mathey D G *et al*

Lahiri A (& Carboni G P, Crawley J W, Raftery E B) Reversible ischaemia of right ventricle detected by exercise thallium-201 scintigraphy 260

Lam W *see* Rich S *et al*

Landmark K (& Sire S, Thaulow E, Amlie J P, Nitter-Hauge S) Haemodynamic effects of nifedipine and propranolol in patients with hypertrophic obstructive cardiomyopathy 19

Langenstein B A *see* Matsumoto M *et al*
    Schlüter M *et al*

Laufer J (& Frand M, Milo S) Valve replacement for severe tricuspid regurgitation caused by Libman-Sacks endocarditis: case report 294

Lavender P *see* Deanfield J E *et al*

Layton C *see* Ilsley C *et al*

Leatham A *see* Dancy M *et al*

Leech G *see* Dancy M *et al*

Leval M de *see* de Leval M

Leval M R de *see* de Leval M R

Lincoln C *see* Shore D F *et al*

Linden R J *see* Elamin M S *et al*

Logan R *see* Riemersma R A *et al*

Lowry P J (& Edwards C W, Nagle R E) Herpes-like virus particles in myocardium of patient progressing to congestive cardiomyopathy: case report 501

Lüdertiz B *see* D'Alnoncourt C N *et al*

Macartney F J *see* Deanfield J E *et al*
    Huhta J C *et al*
    Smallhorn J F *et al*

McCormack R J M *see* Marquis R M *et al*

Mack M *see* Rehr R B *et al*

McKay R (& Stark J, de Leval M) Unusual vascular ring in infant with pulmonary atresia and ventricular septal defect: case report 180

McKenna W J *see* Deanfield J E *et al*
    Rowland E *et al*

Mackintosh A F (& Carmichael D J, Wren C, Cory-Pearce R, English T A H) Sinus node function in first three weeks after cardiac transplantation 584

McMichael J History of atrial fibrillation 1628-1819. Harvey – de Senac – Laënnec 193

McQuaid R *see* Fitzgerald D J *et al*

Mann S (& Altman D G, Raftery E B, Bannister R) Inverted circadian blood pressure rhythm in autonomic failure 91 *P*

Marier D L *see* Sutton M G St J *et al*

Marquis R M (& Miller H C, McCormack R J M, Matthews M B, Kitchin A H) Persistence of ductus arteriosus with left to right shunt in the older patient 469

Martinez J *see* Rich S *et al*

Mary D A S G *see* Elamin M S *et al*

Maslowski A H *see* Ikram H *et al*

Mathey D G (& Schofer J, Kuck K-H, Beil U, Klöppel G) Transmural, haemorrhagic myocardial infarction after intracoronary streptokinase. Clinical, angiographic, and necropsy findings 546

Matsumoto M (& Hanrath P, Kremer P, Tams C, Langenstein B A, Schlüter M, Weiter R, Bleifeld W) Evaluation of left ventricular performance during supine exercise by transoesophageal M-mode echocardiography in normal subjects 61

– (& Strom J, Hirose H, Abe H) Preoperative echocardiographic diagnosis of anterior mitral valve leaflet fenestration associated with infective endocarditis 538

Mattheos M *see* Oldershaw P J *et al*

Matthews M B *see* Marquis R M *et al*

Mayr A *see* Hofstetter R *et al*

Meade T W *see* Greenberg G *et al*

Melvin K R (& Pollick C P, Wallwork J, Stinson E B) Orthotopic vs. heterotopic cardiac transplantation: haemodynamic and physiological factors 90 *P*

Meltzer R S *see* Verheugt F W A *et al*

Messmer B J *see* Schweizer P *et al*

Metcalffe J (& Somerville J) Early and late results of surgical repair of lesions associated with corrected transposition 94 *P*

Metras D (& Coulibaly A O, Ouattara K) Calcified unruptured aneurysm of sinus of Valsalva with complete heart block and aortic regurgitation. Successful repair in one case: case report 507

Miettinen O S *see* Hofman A *et al*

Milanesi O (& Thiene G, Bini R M, Pellegrino P A) Complete transposition of great arteries with coarctation of aorta 566

Miller H C *see* Marquis R M *et al*

Mills P Reliability and clinical relevance of detection of vegetations by echocardiography in bacterial endocarditis: correspondence 83

Milo S *see* Laufer J *et al*

Minale C *see* Schweizer P *et al*

Mitchell J R A Theory and practice in prevention of arterial thrombosis: editorial 417

Miyatake K (& Nimura Y, Sakakibara H, Kinoshita N, Okamoto M, Nagata S, Kawazoe K, Fujita T) Localisation and direction of mitral regurgitant flow in mitral orifice studied with combined use of ultrasonic pulsed Doppler technique and two dimensional echocardiography 449

Mo H Vik- *see* Vik-Mo H

Moerman P *see* Van der Hauwaert L G *et al*

Moleiro F *see* Castellanos A *et al*

Morrell P (& Sutherland G R, Bain H H, Hunter S) Complications of long-term prostaglandin E_2 therapy in infants with complex heart disease 95 *P*

Morrice J *see* Williams K N *et al*

Morton P *see* Keenan D J M *et al*

Motro M *see* Eldar M *et al*

Muir A L *see* Forfar J C *et al*

Musumeci F *see* Dickinson D F *et al*

Myerburg R J *see* Castellanos A *et al*

Nagata S *see* Miyatake K *et al*

Nagle R E *see* Lowry P J *et al*

Nakamura Y *see* Yamazaki H *et al*

Nathan A W (& Hellestrand K J, Bexton R S, Ward D E, Spurrell R A J, Camm A J) Electrophysiological effects of sotalol—more than just another beta blocker 88 *P*

– *see also* Hellestrand K J *et al*

Nelson G I C *see* Silke B *et al*

Neufeld H N *see* Eldar M *et al*

Newburger J *see* Hofman A *et al*

Nicholls M G *see* Ikram H *et al*

Nimura Y *see* Miyatake K *et al*

Nishimura R A (& Shub C, Tajik A J) Two dimensional echocardiographic diagnosis of partial papillary muscle rupture: case report 598

Nitter-Hauge S *see* Landmark K *et al*
    Thaulow E *et al*

Norell M *see* Bayliss J *et al*

Nunan T O *see* Joy M *et al*

Oakley C M *see* Davies J *et al*

O'Brien E *see* Fitzgerald D J *et al*

O'Callaghan W G *see* Fitzgerald D J *et al*

Ohsuzu F *see* Yamazaki H *et al*

Okamoto M *see* Miyatake K *et al*

O'Kane H O *see* Keenan D J M *et al*
    Pringle T H *et al*

Oldershaw P J (& Shapiro E, Mattheos M, Sutton M G St J, Gibson D) Independence of changes in left ventricular diastolic properties of pericardial pressure 125

– *see also* Sutton M G St J *et al*

Oliver M F *see* Riemersma R A *et al*

Olsen E G J *see* Daly K *et al*
    Donaldson R M *et al*

O'Malley K *see* Fitzgerald D J *et al*

Ouattara K *see* Metras D *et al*

Parimelazhagan KM *see* Dickinson D F *et al*

Parnham A J *see* Jennings K *et al*

Partridge J B *see* Gerlis L M *et al*

Pattison J *see* Daly K *et al*

Pearce R Cory- *see* Cory-Pearce R

Pefkaros K *see* Castellanos A *et al*

Pellegrino P A *see* Milanesi O *et al*

Peploe M M Webb- *see* Webb-Peploe M M

Picchio F M *see* Bonvicini M *et al*

Piccoli G P *see* Dickinson D F *et al*

Piovaccari G *see* Bonvicini M *et al*

Pollard C M *see* Joy M *et al*

Pollick C P *see* Melvin K R *et al*

Polster J *see* Schlüter M *et al*

Poole-Wilson P A *see* Bayliss J *et al*
    Ilsley C *et al*

Pringle T H (& Webb S W, Khan M M, O'Kane H O J, Cleland J, Adgey A A J) Clinical echocardiographic, and operative findings in active infective endocarditis 529

Qadt F J A *see* Stoel I *et al*

Raftery E B *see* Lahiri A *et al*
    Mann S *et al*

Rath S *see* Eldar M *et al*

Rees J R *see* Walker P R *et al*

Rehr R B (& Mack M, Firth B G) Aortic regurgitation and sinus of Valsalva-right atrial fistula after blunt thoracic trauma: case report 410

Reid D S *see* Jennings K *et al*
Reid J L *see* Rodger J C *et al*
Reid J M (& Coleman E N, Doig W) Complete congenital heart block. Report of 35 cases 236
Reidy J F (& Deverall P B, Sowton E) Successful late non-surgical removal of intracardiac catheter fragment: case report 407
Restivo A (& Ho S Y, Anderson R H, Cameron H, Wilkinson J L) Absent left atrioventricular connection with right atrium connected to morphologically left ventricular chamber, rudimentary right ventricular chamber, and ventriculoarterial discordance. Problem of mitral versus tricuspid atresia 240
Reuben S *see* Bayliss J *et al*
Ribero P *see* Fox K M *et al*
Rich S (& Martinez J, Lam W, Rosen K M) Captopril as treatment for patients with pulmonary hypertension. Problem of variability in assessing chronic drug treatment 272
Richardson P J (& Wodak A, Atkinson L, Jewitt D E) Relation between alcohol intake, myocardial dysfunction, and myocardial tissue enzyme activities 93 *P*
– *see also* Daly K *et al*
Rickards A F *see* Donaldson R M & Rickards A F
Donaldson R M *et al*
Ilsley C *et al*
Riemersma R A (& Logan R, Russell D C, Smith H J, Simpson J, Oliver M F) Effect of heparin on plasma free fatty acid concentrations after acute myocardial infarction 134
Rigby M L *see* Shore D F *et al*
Rodger J C (& Struthers A D, Whitesmith R, Reid J L) Changes in plasma potassium and the electrocardiogram induced by adrenaline and the effect of beta blockade on them 91 *P*
Roelandt J *see* Verheugt F W A *et al*
Rootwelt K *see* Thaulow E *et al*
Rosen K M *see* Bauernfeind R A *et al*
Rich S *et al*
Ross D N *see* Donaldson R M *et al*
Rowe R D *see* Freedom R M *et al*
Rowland E (& McKenna W, Krikler D M) Comparative electrophysiological effects of novel antiarrhythmic drug, bepridil 87 *P*
Rozanski J J *see* Castellanos A *et al*
Russell D C *see* Riemersma R A *et al*
Rutishauser W *see* Benmimoun E G *et al*

Sacchetti R *see* Sutton M G St J *et al*
Sakakibara H *see* Miyatake K *et al*
Saltups A *see* Gelman J S & Saltups A
Schaffer M S *see* Freedom R M *et al*
Scheck H *see* Verheugt F W A *et al*
Schlüter M (& Langenstein B A, Polster J, Kremer P, Souquet J, Engel S, Hanrath P) Transoesophageal cross-sectional echocardiography with a phased array transducer system. Technique and initial clinical results 67
– *see also* Matsumoto M *et al*
Schofer J *see* Mathey D G *et al*
Schultze G *see* Sehested J & Schultze G
Schweizer P (& Bardos P, Krebs W, Erbel R, Minale C, Imm S, Messmer B J, Effert S) Morphometric investigations in mitral stenosis using two dimensional echocardiography 54
Schy N *see* Eldar M *et al*
Sehested J (& Schultze G) Vasomotor wave and blood pressure response to erect posture after operation for aortic coarctation 357
Shahar J *see* Abinader E G and Shahar J
Shapiro E *see* Oldershaw P J *et al*
Shaw D B *see* Veale D *et al*
Shaw T R D Removal of embolised catheters using flexible endoscopy forceps 497
Shore D F (& Rigby M L, Lincoln C) Severe tricuspid stenosis presenting as tricuspid atresia. Echocardiographic diagnosis and surgical management 404
– (& Smallhorn J, Stark J, Lincoln C, de Leval M R) Left ventricular outflow tract obstruction coexisting with ventricular septal defect 421
Short D *see* Beach C *et al*
Shub C *see* Nishimura R A *et al*
Silke B (& Nelson G I C, Ahuja R C, Taylor S H) Comparative haemodynamic dose response effects of propranolol and labetalol in coronary heart disease 364
Silove E D *see* de Giovanni J V *et al*
Simpson J *see* Riemersma R A *et al*
Sire S *see* Landmark K *et al*
Skrinskas G *see* Baron M *et al*
Slutsky R *see* Watkins J *et al*
Smallhorn J F (& Anderson R H, Macartney F J) Cross-sectional echocardiographic recognition of interruption of aortic arch between left carotid and subclavian arteries 229
– (& de Leval M, Stark J, Somerville J, Taylor J F N, Anderson R H, Macartney F J) Isolated anterior mitral cleft. Two dimensional echocardiographic assessment and differentiation from "clefts" associated with atrioventricular septal defect 109
– (& Huhtra J, Anderson R H, Macartney F J) Role of suprasternal two dimensional echocardiography in assessment of neonate and infant with congenital heart disease 95 *P*
– (& Huhta J C, Anderson R H, Macartney F J) Suprasternal cross-sectional echocardiography in assessment of patent ductus arteriosus 321
– (& Sutherland G R, Anderson R H, Macartney F J) Cross-sectional echocardiographic assessment of conditions with atrioventricular valve leaflets attached to the atrial septum at the same level 331
– *see also* Huhta J C *et al*
Shore D F *et al*
Smith D R *see* Elamin M S *et al*
Young M A & Smith D R
Smith G H *see* Goiti J J & Smith G H
Smith H J *see* Riemersma R A *et al*
Smith K Hallidie- *see* Hallidie-Smith K
Snell N J C *see* Bell J A *et al*
Soloff L A Electrocardiogram of pure left ventricular hypertrophy and its differentiation from lateral ischaemia: correspondence 85
Somerville J *see* Metcalffe J & Somerville J
Smallhorn J F *et al*
Souquet J *see* Schlüter M *et al*
Sowton E *see* Reidy J F *et al*
Spry C J F *see* Davies J *et al*
Spurrell R A J *see* Bexton R S *et al*
Hellestrand K J *et al*
Nathan A W *et al*
Stark J *see* McKay R *et al*
Shore D F *et al*
Smallhorn J F *et al*
Stinson E B *see* Melvin K R *et al*
Stockley A *see* Ilsley C *et al*
Stoel I (& Giessen W J v d, Zwolsman E, Verheugt F W A, ten Hoor F, Quadt F J A, Hugenholtz P G) Effect of nicotine on production of prostacyclin in human umbilical artery 493
Stoker J B *see* Elamin M S *et al*
Stone P C W *see* Voulgari F *et al*
Strasberg B *see* Bauernfeind R A *et al*
Strom J *see* Matsumoto M *et al*
Struthers A D *see* Rodger J C *et al*
Stuart J *see* Voulgari F *et al*
Sugrue D *see* Deanfield J E *et al*
Sutherland G *see* Evemy K *et al*
Sutherland G R *see* Morrell P *et al*
Smallhorn J F *et al*
Sutton G C *see* Bayliss J *et al*
Sutton M G St J (& Marier D L, Oldershaw P J, Sacchetti R, Gibson D G) Effect of age related changes in chamber size,

wall thickness, and heart rate on left ventricular function in normal children 342
– *see also* Oldershaw P J *et al*
Swanton R H *see* Walton S *et al*

Tajik A J *see* Nishimura R A *et al*
Takagi Y *see* Yamazaki H *et al*
Talabi A I *see* George B O *et al*
Tams C *see* Matsumoto M *et al*
Taylor J F N *see* Smallhorn J F *et al*
Taylor S H *see* Silke B *et al*
Ten Hoor F *see* Stoel I *et al*
Thaulow E (& Rootwelt K, Erikssen J, Nitter-Hauge S) Routine radionuclide techniques in evaluation of patients with suspected coronary heart disease 255
– *see also* Landmark K *et al*
Thiene G *see* Milanesi O *et al*
Thomas J M *see* Bell J A *et al*
Thompson D S *see* Wilmshurst P T *et al*
Toft A D *see* Forfar J C *et al*
Tommasini G *see* Deanfield J E *et al*
Traill T A (& Fortuin N J) Presystolic mitral closure sound in aortic regurgitation with left ventricular hypertrophy and first degree heart block: case report 78
Tsugu T *see* Yamazaki H *et al*
Tubau J *see* Watkins J *et al*
Tweedie M C K *see* Dickinson D F *et al*

Urowitz M B *see* Baron M *et al*

Van der Hauwaert L G (& Dumoulin M, Moerman P) Congenital atresia of left coronary ostium: case report 298
Van Doesburg N *see* Fouron J C *et al*
Vanhees L (& Fagard R, Amery A) Influence of beta adrenergic blockade on effects of physical training in patients with ischaemic heart disease 33
Veale D (& Kekwick C A, Gowers J, Whistance A, Shaw D B) Prognosis of chronic second degree atrioventricular block 87 *P*
Verheugt F W A (& Scheck H, Meltzer R S, Roelandt J) Alternating atrial electromechanical dissociation as contributing factor for pulsus alternans 459
– *see also* Stoel I *et al*
Vik-Mo H *see* Andersen K and Vik-Mo H
Von Bernuth G *see* Hofstetter R *et al*
Voulgari F (& Cummins P, Gardecki T I M, Beeching N J, Stone P C W, Stuart J) Serum levels of acute phase and cardiac proteins after myocardial infarction, surgery, and infection 352

Walker P R (& Davies E R, Watt I, Rees J R) Comparison of "dipyridamole-exercise" thallium-201 imaging and standard exercise thallium-201 imaging in men with angina 89 *P*
Wallwork J *see* Melvin K R *et al*
Walton S (& Ell P J, Jarritt P H, Swanton R H) Phase analysis of the first pass radionuclide angiocardiogram 441
Ward D E *see* Nathan A W *et al*
Watanabe Y (& Kishi H) Permanent right bundle-branch block heralded by intermittent block and ventricular extrasystoles. A 13-year observation: case report 184
Watkins J (& Slutsky R, Tubau J, Karliner J) Scintigraphic study of relation between left ventricular peak systolic pressure and end-systolic volume in patients with coronary artery disease and normal subjects 39
Watt I *see* Walker P R *et al*
Webb S *see* Ilsley C *et al*
Webb S W *see* Pringle T H *et al*
Webb-Peploe M M *see* Williams K N *et al*
Wilmshurst P T *et al*
Weiter R *see* Matsumoto M *et al*
Wenink A C G (& Gittenberger-de Groot A C) Left and right ventricular trabecular patterns. Consequence of ventricular septation and valve development 462
West C R *see* Dickinson D F *et al*
Westgate C *see* Ilsley C *et al*
Whistance A *see* Veale D *et al*
Whitaker W *see* Elamin M S *et al*
Whitesmith R *see* Rodger J C *et al*
Wilcken D E L *see* Hickey A J *et al*
Wilkinson J L *see* Restivo A *et al*
Williams K N (& Brooksby I A B, Morrice J, Houseago S, Webb-Peploe M M) Computerised cardiological case notes 169
Wilmshurst P T (& Thompson D S, Jenkins B S, Coltart D J, Webb-Peploe M M) Effect of intravenous amrinone on resting haemodynamic function in patients with congestive cardiac failure 93 *P*
Wilson P Poole- *see* Poole-Wilson P
Wodak A *see* Richardson P J *et al*
Wolfers J *see* Hickey A J *et al*
Wren C *see* Mackintosh A F *et al*
Wright C *see* Fox K M *et al*

Yacoub M *see* Donaldson R M *et al*
Yamazaki H (& Tsugu T, Handa S, Takagi Y, Ohsuzu F, Kondo M, Kubo A, Inoue T, Nakamura Y) Postoperative thallium-201 myocardial images. Evidence of regression of right ventricular hypertrophy in man 372
Young M A (& Smith D R) Oxford pacemaker infection trial: correspondence 306

Zema M J (& Caccavano M) Two dimensional echocardiographic assessment of aortic valve morphology: feasibility of bicuspid valve detection. Prospective study of 100 adult patients 428
Zierhut W *see* D'Alnoncourt C N *et al*
Zwolsman E *see* Stoel I *et al*

SUBJECT INDEX

1982, Volume 48

Absent left atrioventricular connection, four cases, problem of mitral versus tricuspid atresia (Restivo *et al*). 240
Acute phase proteins, serum levels after myocardial infarction, surgery and infection (Voulgari *et al*). 352
Adrenaline-induced changes in plasma potassium and the ECG, and effect of beta blockade (Rodger *et al*). 91 *P*
Age related changes in chamber size, wall thickness and heart rate, effects on left ventricular function in normal children (Sutton *et al*). 342
Alcohol intake, myocardial dysfunction, and myocardial tissue enzyme activities (Richardson *et al*). 93 *P*
Amrinone, intravenous, effect on resting haemodynamic function in congestive cardiac failure (Wilmshurst *et al*). 93 *P*
Aneurysm of sinus of Valsalva, calcified unruptured, with complete heart block and aortic regurgitation: case report (Metras *et al*). 507
Aneurysmal tissue tag complicating an infundibular perimembranous ventricular septal defect (Bonvicini *et al*). 189
Angina pectoris
  dipyridamole-exercise "thallium-201 imaging compared with standard thallium-201 imaging (Walker *et al*). 89 *P*
  diurnal variation in exercise responses (Joy *et al*). 156
Antiarrhythmic drug, bepridil, comparative electrophysiological effects (Rowland *et al*). 87 *P*
Aortic
  arch, interruption between left carotid and subclavian arteries, cross-sectional echocardiography recognition (Smallhorn *et al*). 229
  coarctation operation, vasomotor wave and blood pressure response to erect posture after (Sehested & Schultze). 357
  regeneration, changes in left ventricular mass, volume, and function after surgery for (Donaldson *et al*). 92 *P*
  regurgitation, chronic, irreversible morphological changes contributing to depressed cardiac function after surgery (Donaldson *et al*). 589
    and sinus of Valsalva-right atrial fistula after blunt thoracic trauma: case report (Rehr *et al*). 410
    with left ventricular hypertrophy, presystolic mitral closure sound in, and first degree heart block: case report (Traill & Fortuin). 78
  valve morphology, 2-D echo assessment, feasibility of bicuspid valve detection (Zema & Caccavano). 428
    systolic closure in patients with prosthetic mitral valves (Eldar *et al*). 48
Arrhythmias
  cardiac, in hypertrophic cardiomyopathy (Bjarnason *et al*). 198
  ventricular, in tetralogy of Fallot (Deanfield *et al*). 88 *P*
Arterial thrombosis, theory and practice: editorial (Mitchell). 417
Atenolol, oral, role of Frank-Starling mechanism during maximal semisupine exercise after (Andersen & Vik-Mo) 149
Atrial
  appendage, left, anomalous connection with persistent left superior vena cava: case report (Gerlis *et al*). 73
  electromechanical dissociations, alternating, as contributing factor for pulsus alternans (Verheught *et al*). 459
  fibrillation, history, 1628-1819 (McMichael). 193
  myxoma, right, large calcified, newborn: case report (Dianzumba & Char). 177
  myxoma, right and pulmonary embolism: case report (Keenan *et al*). 510
  pacing, increased, in heart transplant rejection (Cory-Pearce *et al*). 89 *P*
Atrioventricular
  block, chronic second degree, prognosis (Veale *et al*). 87 *P*
  valve leaflets attached to atrial septum at same level, cross-sectional echocardiographic assessment (Smallhorn *et al*). 331
Autonomic failure, inverted circadian blood pressure rhythm (Mann *et al*). 91 *P*

Bacterial endocarditis, detection of vegetations by echocardiography: correspondence (Mills: Hickey *et al*). 83
Bepridil, comparative electrophysiological effects (Rowland *et al*). 87 *P*
Beta blockade
  diastolic function in HCM on and off (Alvares & Goodwin). 204
  effect on changes in plasma potassium and the ECG induced by adrenaline (Rodger *et al*). 91 *P*
  and exercise in left ventricular function in hypothyroidism (Forfar *et al*). 278
  exercise testing in mitral valve prolapse before and after (Abinader & Shahar). 130
  influence on physical training in ischaemic heart disease (Vanhees *et al*). 33
Blood pressure
  and endogenous progesterone (Greenberg *et al*). 92 *P*
  and haemodynamics in teenagers (Hofman *et al*). 377
  inverted circadian rhythm, in autonomic failure (Mann *et al*). 91 *P*
  recorders, ambulatory, accuracy and reliability (Fitzgerald *et al*). 572
  and vasomotor wave response to erect posture after aortic coarctation operation (Sehested & Schultze). 357
Bundle-branch block
  complete right, significance when an isolated finding, echocardiography (Dancy *et al*). 217
  functional, slowing of paroxysmal tachycardia with loss of: case report (Bauernfeind *et al*). 75
  permanent, right, heralded by intermittent block and ventricular extrasystoles: case report (Watanabe & Kishi). 184

Calcified unruptured aneurysm of sinus of Valsalva with complete heart block and aortic regurgitation: case report (Metras *et al*). 507
Cannulation, coronary artery in measurement of pulmonary artery pressure in cyanotic heart disease: case report (Dillon). 504
Captopril in pulmonary hypertension (Rich *et al*). 272
  haemodynamic and hormonal effects (Ikram *et al*). 541
Cardiac
  ischaemia *see* Ischaemic heart disease
  transplantation, *see* Heart transplantation
Cardiodyne Sphygmolog, ambulatory blood pressure recorder, accuracy and reliability (Fitzgerald *et al*). 572
Cardiomyopathy
  in Friedreich's ataxia (de Giovanni *et al*). 92 *P*
  frontiers (Goodwin). 1
  hypertrophic, *see* Hypertrophic cardiomyopathy
Cardiovascular disease, immunological probes: correspondence (Jennings *et al*). 604

- Catheter
  - embolised, removal using flexible endoscopy forceps (Shaw). 497
  - intracardiac fragment, successful late non-surgical removal: case report (Reidy *et al*). 407
- Chest injury causing aortic regurgitation and sinus of Valsalva-right atrial fistula: case report (Rehr *et al*). 410
- Coarctation of aorta with complete transposition of great arteries (Milanesi *et al*). 566
- Computer analysis, cardiac contractility variables, M-mode echocardiography, normal newborns (Hofstetter *et al*). 525
- Computerised cardiological case notes (Williams *et al*). 169
- Conduction, cardiac, effect of flecainide acetate (Hellestrand *et al*). 140
- Congenital
  - complete heart block, 35 cases (Reid *et al*). 236
  - heart disease, neonate and infant, two-dimensional suprasternal echocardiography in assessment (Smallhorn *et al*). 95 *P*
- Congestive cardiomyopathy, after herpes-like virus particles in myocardium: case report (Lowry *et al*). 501
- Contractility variables, cardiac, computer analysis of M-mode echocardiograms, normal newborns (Hofstetter *et al*). 525
- Coronary
  - arteriogram, normal, evaluation (Ilsley *et al*). 580
  - artery cannulation in measurement of pulmonary artery pressure in cyanotic heart disease: case report (Dillon). 504
    - disease, diltiazem compared with nifedipine in (Kenny *et al*). 89 *P*
      - exercise heart rate/ST segment relation as perfect predictor: editorial (Fox). 309
      - exercise testing and ST segment in accurate detection (Elamin *et al*). 311
      - scintigraphic study, relation between left ventricular peak systolic pressure and end-systolic volume, and in normal (Watkins *et al*). 39
      - propranolol and labetalol in, comparative haemodynamic dose response (Silke *et al*). 364
    - suspected, routine radionuclide techniques in evaluation (Thaulow *et al*). 255
    - narrowing without irreversible myocardial damage or development collaterals (Falk) 265
    - spasm and mitral valve prolapse: correspondence (Cheng: Huckell). 301
    - surgery using inverted internal mammary artery: case report (Goiti & Smith). 81
  - care, home, trial of prophylactic mexiletine (Bell *et al*). 285
  - ostium, left, congenital atresia: case report (van der Hauwaert *et al*). 298
- Correspondence
  - Echocardiographic diagnosis of isolated pulmonary valve endocarditis (Brown *et al*). 307
  - Echocardiographic dimensions (Anderson). 605
  - Effects of prostaglandin E_1 and other vasodilator agents in pulmonary hypertension of scleroderma (Baron *et al*: Ikram). 304
  - Electrocardiogram of pure left ventricular hypertrophy and its differentiation from lateral ischaemia (Soloff: Beach *et al*). 85
  - Hang-out time of pulmonary valve in d-transposition of great arteries (Anderson: Fouron *et al*). 302
  - Immunological probes in cardiovascular disease (Jennings *et al*). 604
  - Mitral valve prolapse and coronary artery spasm (Cheng: Huckell). 301
  - Oxford pacemaker infection trial (Young and Smith). 306
  - Reliability and clinical relevance of detection of vegetables by echocardiography in bacterial endocarditis (Mills: Hickey *et al*). 83
- Cyanotic heart disease, measurement of pulmonary artery pressure using selective coronary artery cannulation techniques: case report (Dillon). 504
- Diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs (Alvares & Goodwin). 204
- Digitalis-induced atrial tachycardia, effects of lignocaine (Castellanos *et al*). 27
- Digoxin toxicity, Fab treatment: correspondence (Jennings *et al*). 604
- Diltiazem compared with nifedipine in coronary artery disease (Kenny *et al*). 89 *P*
- Dipyridamole-exercise thallium-201 imaging and standard exercise thallium-201 imaging in angina (Walker *et al*). 89 *P*
- Disopyramide phosphate, direct physiological effects, evaluated in denervated heart (Bexton *et al*). 87 *P*
- Doppler technique combined with 2-D echocardiography in study of mitral regurgitant flow in mitral orifice (Miyatake *et al*). 449
- Drug-induced changes, evaluation in myocardial repolarisation using paced evoked response (Donaldson : Rickards). 381

- Echocardiography
  - in anterior mitral valve leaflet fenestration associated with infective endocarditis (Matsumoto *et al*). 538
  - cross-sectional, diagnosis of systemic venous return (Huhta *et al*). 388
    - in interruption of aortic arch between left carotid and subclavian arteries (Smallhorn *et al*). 229
    - in patients with atrioventricular valve leaflets attached to atrial septum at same level (Smallhorn *et al*). 331
    - suprasternal, in assessment of patent ductus arteriosus (Smallhorn *et al*). 321: 95 *P*
  - detection of vegetations in bacterial endocarditis: correspondence (Mills: Hickey *et al*). 83
  - diagnosis of isolated pulmonary valve endocarditis: correspondence (Brown *et al*). 307
  - dimensions: correspondence (Anderson). 605
  - in eosinophilic endomyocardial disease (Davies *et al*). 434
- M-mode computer analysis, normal newborns (Hofstetter *et al*). 525
    - endomyocardial fibrosis (George *et al*). 222
  - transoesophageal, in evaluation of left ventricular performance during exercise, normal subjects (Matsumoto *et al*). 61
    - with phased array transducer system (Schlüter *et al*). 67
  - two-dimensional, assessment of aortic valve morphology, feasibility of bicuspid valve detection (Zema & Caccavano). 428
    - in demonstration of adult interventricular septum (Evemy *et al*). 95 *P*
    - in mitral stenosis (Schweizer *et al*). 54
    - in partial papillary muscle rupture: case report (Nishimura *et al*). 598
    - and pulsed Doppler technique combined in study of mitral regurgitant flow in mitral orifice (Miyatake *et al*). 449
    - in situs (Huhta *et al*). 97
    - suprasternal, role in assessment of neonate and infant congenital heart disease (Smallhorn *et al*). 321: 95 *P*
- Editorial
    - Exercise heart rate/ST segment relation. Perfect predictor of coronary disease (Fox). 309
    - Theory and practice in prevention of arterial thrombosis (Mitchell). 417
- Electrophysiological effects of flecainide acetate on cardiac conduction and refractoriness (Hellestrand *et al*). 140
- Embolised catheters, removal using flexible endoscopy forceps (Shaw). 497
- Endocarditis
  - infective, *see* Infective endocarditis
  - pulmonary valve, echocardiographic diagnosis (Brown *et al*). 307
- Endomyocardial
  - fibrosis, M-mode echocardiography (George *et al*). 222
  - *see also* Eosinophilic endomyocardial disease
- Enzyme activities, myocardial tissue, myocardial dysfunction and alcohol intake, relation between (Richardson *et al*). 93 *P*

- Eosinophilic endomyocardial disease, echocardiographic features (Davies *et al*). 434
- Exercise
  - and beta blockade in left ventricular function in hypothyroidism (Forfar *et al*). 278
  - heart rate/ST segment relation, perfect predictor of coronary disease: editorial (Fox). 309
  - influence of R wave analysis on diagnostic accuracy (Ilsley *et al*). 161
  - maximal semisupine after atenolol, role of Frank-Starling mechanism (Andersen & Vik-Mo). 149
  - in mitral valve prolapse before and after beta blockade (Abinader & Shahar). 130
  - responses, diurnal variation, angina pectoris (Joy *et al*). 156
  - and ST segment, in accurate detection of coronary heart disease (Elamin *et al*). 311
  - and projection of ST segment changes to front of chest (Fox *et al*). 555
  - supine, transoesophageal M-mode echocardiography in evaluation of left ventricular performance during (Matsumoto *et al*). 61
  - thallium-201 scintigraphy, reversible ischaemia of right ventricle detected by (Lahiri *et al*). 260

- Fatty acids, free, after myocardial infarction, effect of heparin (Riemersma *et al*). 134
- First pass radionuclide angiocardiogram, phase analysis (Walton *et al*). 441
- Flecainide acetate, acute electrophysiological effects on cardiac conduction and refractoriness (Hellestrand *et al*). 140
- Frank-Starling mechanism during maximal semisupine exercise after oral atenolol (Andersen & Vik-Mo). 149
- Friedreich's ataxia, cardiomyopathy (de Giovanni *et al*). 92 *P*

- Haemodynamics and blood pressure in teenagers (Hofman *et al*). 377
- Heart
  - block, complete congenital, 35 cases (Reid *et al*). 236
  - failure, vasodilatation, and inotropism, interaction between (Bayliss *et al*). 93 *P*
  - transplantation, orthoptic vs. heterotopic, haemodynamic and physiological factors (Melvin *et al*). 90 *P*
  - sinus node function in first three weeks (Mackintosh *et al*). 584
  - rejection, increased atrial threshold in (Cory-Pearce *et al*). 89 *P*
- Heparin, effect on plasma free fatty acid concentrations after myocardial infarction (Riemersma *et al*). 134
- Herpes-like virus particles in myocardium progressing to congestive cardiomyopathy: case report (Lowry *et al*). 501
- History of atrial fibrillation, 1628-1819 (McMichael). 193
- Home coronary care, trial of prophylactic mexiletine (Bell *et al*). 285
- Hypertension, pulmonary, primary, captopril in, haemodynamic and hormonal effects (Ikram *et al*). 541
- Hypertrophic cardiomyopathy
  - cardiac arrhythmias in (Bjarnason *et al*). 198
  - on and off beta adrenergic blocking drugs, non-invasive assessment of diastolic function in (Alvares & Goodwin). 204
  - constructive nifedipine and propranolol in, haemodynamic effects (Landmark *et al*). 19
- Hypothyroidism, left ventricular function in, responses to exercise and beta blockade (Forfar *et al*). 278

- Immunological probes in cardiovascular disease: correspondence (Jennings *et al*) 604
- Immunosuppressive therapy in acute inflammatory myocarditis (Daly *et al*). 94 *P*
- Infection
  - Oxford pacemaker trial: correspondence (Young & Smith). 306
  - serum levels of acute phase and cardiac proteins after (Voulgari *et al*). 352
- Infective endocarditis
  - active, clinical, echocardiographic, and operative findings (Pringle *et al*). 529
  - associated with anterior mitral valve leaflet fenestration, preoperative echocardiographic diagnosis (Matsumoto *et al*). 538
- Inotropism and vasodilatation in heart failure, interaction between (Bayliss *et al*). 93 *P*
- Inverted circadian blood pressure rhythm in autonomic failure (Mann *et al*). 91 *P*
- Interventricular septum, defects, adults, demonstration by two-dimensional echocardiography (Evemy *et al*). 95 *P*
- Ischaemia of right ventricle, reversible, detected by exercise thallium-201 scintigraphy (Lahiri *et al*). 260
- Ischaemic heart disease
  - influence of beta adrenergic blockade on effects of physical training (Vanhees *et al*). 33
  - reversible, and cardiac arrhythmia, relation between (Davies *et al*). 90 *P*
  - sudden versus gradual withdrawal of sotalol in ambulant patients (Henderson & Errington) 552
- Isolated anterior mitral cleft, 2-D echocardiographic assessment (Smallhorn *et al*). 109

- Labetalol and propranolol in coronary heart disease, comparative haemodynamic dose response effects (Silke *et al*). 364
- Left superior vena cava, persistent, anomalous connection of left atrial appendage with: case report (Gerlis *et al*). 73
  - left ventricle *see* Ventricle, left
- Lignocaine, effects on bidirectional tachycardia and on digitalis-induced atrial tachycardia with block (Castellanos *et al*). 27

- Mammary artery, inverted internal, coronary artery surgery using: case report (Goiti & Smith). 81
- Mexiletine, prophylactic, trial in home coronary care (Bell *et al*). 285
- Mitral valve
  - atresia versus tricuspid atresia, absent left atrioventricular connection, four cases (Restivo *et al*). 240
  - leaflet fenestration, anterior, associated with infective endocarditis, preoperative echocardiographic diagnosis (Matsumoto *et al*). 538
  - opening and left ventricular function in massive pulmonary embolism: case report (Bullock & Hall). 413
  - prolapse and coronary artery spasm: correspondence (Cheng: Huckell). 301
    - exercise testing before and after beta blockade (Abinader & Shahar). 130
  - prosthetic, systolic closure of aortic valves in patients with (Eldar *et al*). 48
  - regurgitant flow in mitral orifice studied with combined use of ultrasonic pulsed Doppler technique and 2-D echocardiography (Miyatake *et al*). 449
  - replacement in children (Benmimoun *et al*). 117
  - stenosis, morphometric investigations using 2-D echocardiography (Schweizer *et al*). 54
- M-mode echocardiography, *see* Echocardiography, M-mode
- Myocardial
  - dysfunction, myocardial tissue enzyme activities and alcohol intake, relation between (Richardson *et al*). 93 *P*
  - infarction, effect of heparin on plasma free fatty acid concentrations after (Riemersma *et al*). 134
    - inferior, precordial ST segment depression (Gelman & Saltups). 560
    - serum levels of acute phase and cardiac proteins after (Voulgari *et al*). 352
    - transmural, haemorrhagic, intracoronary streptokinase after clinical, angiographic, and necropsy findings (Mathey *et al*). 546

  repolarisation, evaluation of drug-induced changes using paced evoked response (Donaldson & Rickards). 381
Myocarditis, acute inflammatory, immunosuppressive therapy (Daly *et al*). 94 *P*
Myocardium, herpes-like virus particles in, patient progressing to congestive cardiomyopathy: case report (Lowry *et al*). 501
Myxoma, right atrial
  large calcified, newborn: case report (Dianzumba & Char). 177
  and pulmonary embolism: case report (Keenan *et al*). 510

Nicotine, effect on production of prostacyclin in human umbilical artery (Stoel). 493
Nifedipine
  compared with diltiazem in coronary artery disease (Kenny *et al*). 89 *P*
  and propranolol in hypertrophic obstructive cardiomyopathy, haemodynamic effects (Landmark *et al*). 19
Notices 96, 192, 308, 416, 606

Oxford pacemaker infection trial: correspondence (Young & Smith). 306

Paced evoked response, evaluation of drug-induced changes in myocardial repolarisation (Donaldson & Rickards). 381
Papillary muscle of tricuspid valve, rupture, echocardiography: case reports (Donaldson *et al*). 291: (Nishimura *et al*). 598
Paroxysmal tachycardia, slowing, with loss of functional bundle-branch block: case report (Bauernfeind *et al*). 75
Patent ductus arteriosus, suprasternal cross-sectional echocardiography (Smallhorn *et al*). 321
Pericardial pressure, left ventricular diastolic properties, independence of changes (Odershaw *et al*). 125
Persistent ductus arteriosus, with left to right shunt in older patient (Marquis *et al*). 469
Phase analysis of first pass radionuclide angiocardiogram (Walton *et al*). 441
Physical training in ischaemic heart disease patients, influence of beta adrenergic blockade (Vanhees *et al*). 33
Posture, erect; after aortic coarctation operation, vasomotor wave and blood pressure response (Sehested & Schultze). 357
Potassium, plasma, changes, and the ECG, induced by adrenaline and effect of beta blockade (Rodger *et al*). 91 *P*
Presystolic mitral closure sound in aortic regurgitation with left ventricular hypertrophy and first degree heart block: case report (Traill & Fortuin). 78
Proceedings, British Cardiac Society, 61st Annual General Meeting, Nottingham, 14 and 15 April 1982. 87
Progesterone, endogenous, and blood pressure (Greenberg *et al*). 92 *P*
Propranolol
  and labetalol in coronary heart disease, comparative haemodynamic dose response effects (Silke *et al*). 364
  and nifedipine in hypertrophic obstructive cardiomyopathy, haemodynamic effects (Landmark *et al*). 19
Prostacyclin (prostaglandin E_2)
  in umbilical artery, effect of nicotine on production (Stoel). 493
  long-term, complications, in infants with complex heart disease (Morrell *et al*). 95 *P*
Prostaglandin E_1 effects in pulmonary hypertension of scleroderma: correspondence (Baron *et al*: Ikram). 304
Proteins, acute phase and cardiac, serum levels after myocardial infarction, surgery, and infection (Voulgari *et al*). 352
Pulmonary
  artery pressure, measurement in cyanotic heart disease, using selective coronary artery cannulation techniques; case report (Dillon). 504
  atresia and ventricular septal defect associated with unusual vascular ring, infant: case report (McKay *et al*). 180
  embolism, massive, left ventricular function and mitral valve opening in: case report (Bullock & Hall). 413
    and right atrial myxoma: case report (Keenan *et al*). 510
  hypertension, captopril in (Rich *et al*). 272
    captopril in, haemodynamic and hormonal effects (Ikram *et al*). 541
    of scleroderma, effects of prostaglandin E_1 and other vasodilator agents (Baron *et al*: Ikram). 304
  valve endocarditis, isolated, echocardiographic diagnosis: correspondence (Brown *et al*). 307
Pulsus alternans, alternating atrial electromechanical dissociation as contributing factor (Verheught *et al*). 459

R wave analysis, influence on diagnostic accuracy of exercise, women (Ilsley *et al*). 161
Radionuclide
  angiography, first pass, phase analysis (Walton *et al*). 441
  techniques, routine, in evaluation of suspected coronary heart disease (Thaulow). 255
Recanalisation of coronary arteries, in transmural myocardial infarction using intracoronary streptokinase (Mathey *et al*). 546
Records, cardiological, computerised (Williams *et al*). 169
Refractoriness, cardiac, effect of flecainide acetate (Hellestrand *et al*). 140
Remler M2000, ambulatory blood pressure recorder, accuracy and reliability (Fitzgerald *et al*). 572
Right bundle branch block, right, *see* Bundle branch block

Scleroderma, pulmonary hypertension, effects of prostaglandin E_1 and other vasodilator agents: correspondence (Baron *et al*: Ikram). 304
Sinus
  node function in first three weeks after cardiac transplantation (Mackintosh *et al*). 584
  of Valsalva-right atrial fistula after blunt thoracic trauma: case report (Rehr *et al*). 410
Situs, two-dimensional echocardiography in diagnosis (Huhta *et al*). 97
Smoking, *see also* Nicotine
Sotalol
  electrophysiological effects (Nathan *et al*). 88 *P*
  sudden versus gradual withdrawal in ambulant patients with ischaemic heart disease (Henderson & Errington). 552
ST segment
  changes, projection on front of chest, exercise testing and ambulatory monitoring (Fox *et al*). 555
  depression, precordial, in inferior myocardial infarction (Gelman & Saltups) 560
    reciprocal, relation to exercise-induced ST depression (Jennings *et al*). 90 *P*
  exercise heart rate relation, perfect predictor of coronary disease: editorial (Fox). 309
  and exercise testing in accurate detection of coronary heart disease (Elamin *et al*). 311
Streptokinase, intracoronary, and ransmural haemorrhagic myocardial infarction (Mathey *et al*). 546
Superior vena cava, right, anomalous low insertion: case report (Freedom *et al*). 601
Surgery, serum levels of acute phase and cardiac proteins after (Voulgari *et al*). 352
Systolic
  closure of aortic valve in patients with prosthetic mitral valves (Eldar *et al*). 48
  P/V relation in coronary artery disease and in normal (Watkins *et al*). 39

Tachycardia
  bidirectional, effects of lignocaine (Castellanos *et al*). 27
  paroxysmal, slowing, with loss of functional bundle-branch block: case report (Bauernfeind *et al*). 75
  'torsade de pointes', re-entry or focal activity (D'Alnoncourt *et al*). 213

Teenagers, blood pressure and haemodynamics (Hofman *et al*). 377

Tetralogy of Fallot, ventricular arrhythmia, influence of age, haemodynamic factors and surgery (Deanfield *et al*). 88 *P*

Thallium-201-imaging
  standard, compared with dipyridamole exercise in angina (Walker *et al*). 89 *P*
    myocardial, evidence of regression of right ventricular hypertrophy (Yamazaki *et al*). 372
  scintigraphy, exercise, reversible ischaemia of right ventricle detected by (Lahiri *et al*). 260.

Thrombosis, arterial, theory and practice in prevention: (Mitchell). 417

'Torsade de pointes' tachycardia, re-entry or focal activity (D'Alnoncourt *et al*). 213

Total anomalous pulmonary venous
  connection repair using deep hypothermia and circulatory arrest, 44 consecutive infants (Dickinson *et al*). 249
  return, prenatal damage to vascular bed and extrapulmonary veins (Haworth). 513

Transducer system, phased array, transoesophageal cross-sectional echocardiography with (Schlüter *et al*). 67

Transposition of great arteries
  with coarctation of aorta (Milanesi *et al*). 566
  corrected, early and late results of lesions associated with (Metcalfe & Somerville) 94 *P*
  hang-out time of pulmonary valve: correspondence (Anderson: Fouron *et al*). 302

Tricuspid
  atresia, analysis of coronary artery distribution and ventricular morphology (Deanfield *et al*). 485
  valve, papillary muscle, rupture, echocardiographic diagnosis: case report (Donaldson *et al*). 291
  regurgitation, severe, caused by Libman-Sacks endocarditis, valve replacement: case report (Laufer *et al*). 294
  stenosis, severe, presenting as tricuspid atresia, echo diagnosis, surgical management (Shore *et al*). 404

Tricuspid valve replacement in severe tricuspid regurgitation caused by Libman-Sacks endocarditis: case report (Laufer *et al*). 294

Umbilical artery, prostacyclin in, effect of nicotine on production (Stoel). 493

Vascular ring, infant, with pulmonary atresia and ventricular septal defect: case report (McKay *et al*). 180

Vasodilatation in heart failure and inotropism, interaction between (Baylis *et al*). 93 *P*

Vasodilator agents, effects in pulmonary hypertension of scleroderma: correspondence (Baron *et al*: Ikram). 304

Vasomotor wave and blood pressure response to erect posture after aortic coarctation operation (Sehested & Schultze). 357

Vena cava, right superior, anomalous low insertion (Freedom *et al*). 601

Venous return, systemic, cross-sectional echocardiography diagnosis (Huhta *et al*). 388
  see also Total anomalous pulmonary venous return

Ventricle, ventricular
  arrhythmia in tetralogy of Fallot, influence of age, haemodynamic factors, and surgery (Deanfield *et al*). 88 *P*
  left, diastolic properties, of pericardial pressure, independence of changes (Oldershaw *et al*). 125
    function, age-related changes, normal children (Sutton *et al*). 342
      in hypothyroidism, responses to exercise and beta blockade (Forfar *et al*). 278
      and mitral valve opening in massive pulmonary embolism: case report (Bullock & Hall). 413
      presystolic mitral closure sound in aortic regurgitation with, and first degree heart block: case report (Traill & Fortuin). 78
    hypertrophy, electrocardiogram, differentiation from lateral ischaemia: correspondence (Soloff: Beach *et al*). 85
    mass, volume and function, changes after surgery for chronic aortic regurgitation (Donaldson *et al*). 92 *P*
    outflow tract obstruction coexisting with ventricular septal defect (Shore *et al*). 421
    performance, evaluation during exercise by transoesophageal M-mode echocardiography, normal subjects (Matsumoto *et al*). 61
  right hypertrophy, postoperative thallium-201 myocardial images (Yamazaki *et al*). 372
    ischaemia, reversible, detected by exercise thallium-201 scintigraphy (Lahiri *et al*). 260
    obstruction, severe, caused by aneurysmal tissue tag complicating an infundibular perimembranous VSD: case report (Bonvicini *et al*). 189
  septal defect coexisting with left ventricular outflow tract obstruction (Shore *et al*). 421
    inlet, cross-sectional echocardiography in (Smallhorn *et al*). 331
    and pulmonary atresia, associated with unusual vascular ring: infant: case report (McKay *et al*). 180
  trabecular patterns, left and right, consequence of ventricular septation and valve development (Wenink *et al*). 462

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CONTENTS OF VOLUME 48

Number 1

THE FRONTIERS OF CARDIOMYOPATHY John F Goodwin 1

HAEMODYNAMIC EFFECTS OF NIFEDIPINE AND PROPRANOLOL IN PATIENTS WITH HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY K Landmark, S Sire, E Thaulow, J P Amlie, S Nitter-Hauge 19

EFFECTS OF LIGNOCAINE ON BIDIRECTIONAL TACHYCARDIA AND ON DIGITALIS-INDUCED ATRIAL TACHYCARDIA WITH BLOCK A Castellanos, J Ferreiro, K Pefkaros, J J Rozanski, F Moleiro, R J Myerburg 27

INFLUENCE OF BETA ADRENERGIC BLOCKADE ON EFFECTS OF PHYSICAL TRAINING IN PATIENTS WITH ISCHAEMIC HEART DISEASE L Vanhees, R Fagard, A Amery 33

SCINTIGRAPHIC STUDY OF RELATION BETWEEN LEFT VENTRICULAR PEAK SYSTOLIC PRESSURE AND END-SYSTOLIC VOLUME IN PATIENTS WITH CORONARY ARTERY DISEASE AND NORMAL SUBJECTS J Watkins, R Slutsky, J Tubau, J Karliner 39

SYSTOLIC CLOSURE OF AORTIC VALVE IN PATIENTS WITH PROSTHETIC MITRAL VALVES M Eldar, M Motro, S Rath, N Schy, H N Neufeld 48

MORPHOMETRIC INVESTIGATIONS IN MITRAL STENOSIS USING TWO DIMENSIONAL ECHOCARDIOGRAPHY P Schweizer, P Bardos, W Krebs, R Erbel, C Minale, S Imm, B J Messmer, S Effert 54

EVALUATION OF LEFT VENTRICULAR PERFORMANCE DURING SUPINE EXERCISE BY TRANSOESOPHAGEAL M-MODE ECHOCARDIOGRAPHY IN NORMAL SUBJECTS M Matsumoto, P Hanrath, P Kremer, C Tams, B A Langenstein, M Schlüter, R Weiter, W Bleifeld 61

TRANSOESOPHAGEAL CROSS-SECTIONAL ECHOCARDIOGRAPHY WITH PHASED ARRAY TRANSDUCER SYSTEM. TECHNIQUE AND INITIAL CLINICAL RESULTS M Schlüter, B A Langenstein, J Polster, P Kremer, J Souquet, S Engel, P Hanrath 67

CASE REPORTS 73, 75, 78, 81

CORRESPONDENCE 83

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY 87

Number 2

TWO DIMENSIONAL ECHOCARDIOGRAPHIC DIAGNOSIS OF SITUS
J C Huhta, J F Smallhorn, F J Macartney 97

ISOLATED ANTERIOR MITRAL CLEFT. TWO DIMENSIONAL ECHOCARDIOGRAPHIC ASSESSMENT AND DIFFERENTIATION FROM "CLEFTS" ASSOCIATED WITH ATRIOVENTRICULAR SEPTAL DEFECT
J F Smallhorn, M de Leval, J Stark, J Somerville, J F N Tayor, R H Anderson, F J Macartney 109

MITRAL VALVE REPLACEMENT IN CHILDREN. COMPARATIVE STUDY OF PRE- AND POSTOPERATIVE HAEMODYNAMICS AND LEFT VENTRICULAR FUNCTION
E G Benmimoun, B Friedli, W Rutishauser, B Faidutti 117

INDEPENDENCE OF CHANGES IN LEFT VENTRICULAR DIASTOLIC PROPERTIES OF PERICARDIAL PRESSURE
P J Oldershaw, E Shapiro, M Mattheos, M G St John Sutton, D Gibson 125

EXERCISE TESTING IN MITRAL VALVE PROLAPSE BEFORE AND AFTER BETA BLOCKADE
E G Abinader, J Shahar 130

EFFECT OF HEPARIN ON PLASMA FREE FATTY ACID CONCENTRATIONS AFTER ACUTE MYOCARDIAL INFARCTION R A Riemersma, R Logan, D C Russell, H J Smith, J Simpson, M F Oliver 134

ACUTE ELECTROPHYSIOLOGICAL EFFECTS OF FLECAINIDE ACETATE ON CARDIAC CONDUCTION AND REFRACTORINESS IN MAN K J Hellestrand, R S Bexton, A W Nathan, R A J Spurrell, A J Camm 140

ROLE OF THE FRANK-STARLING MECHANISM DURING MAXIMAL SEMISUPINE EXERCISE AFTER ORAL ATENOLOL K Andersen, H Vik-Mo 149

DIURNAL VARIATION IN EXERCISE RESPONSES IN ANGINA PECTORIS M Joy, C M Pollard, T O Nunan 156

INFLUENCE OF R WAVE ANALYSIS UPON DIAGNOSTIC ACCURACY OF EXERCISE TESTING IN WOMEN
C Ilsley, R Canepa-Anson, C Westgate, S Webb, A Rickards, P Poole-Wilson 161

COMPUTERISED CARDIOLOGICAL CASE NOTES
K N Williams, I A B Brooksby, J Morrice, S Houseago, M M Webb-Peploe 169

CASE REPORTS 177, 180, 184, 189

NOTICES 192

Number 3

HISTORY OF ATRIAL FIBRILLATION 1628-1819 HARVEY - DE SENAC - LAËNNEC John McMichael 193

CARDIAC ARRHYTHMIAS IN HYPERTROPHIC CARDIOMYOPATHY I Bjarnason, T Hardarson, S Jonsson 198

NON-INVASIVE ASSESSMENT OF DIASTOLIC FUNCTION IN HYPERTROPHIC CARDIOMYOPATHY ON AND OFF BETA ADRENERGIC BLOCKING DRUGS R F Alvares, J F Goodwin 204

"TORSADE DE POINTES" TACHYCARDIA. RE-ENTRY OR FOCAL ACTIVITY? C Naumann D'Alnoncourt, W Zierhut, B Lüderitz 213

SIGNIFICANCE OF COMPLETE RIGHT BUNDLE-BRANCH BLOCK WHEN AN ISOLATED FINDING. AN ECHOCARDIOGRAPHIC STUDY M Dancy, G Leech, A Leatham 217

M-MODE ECHOCARDIOGRAPHIC FEATURES OF ENDOMYOCARDIAL FIBROSIS B O George, F E Gaba, A I Talabi 222

CROSS-SECTIONAL ECHOCARDIOGRAPHIC RECOGNITION OF INTERRUPTION OF AORTIC ARCH BETWEEN LEFT CAROTID AND SUBCLAVIAN ARTERIES J F Smallhorn, R H Anderson, F J Macartney 229

COMPLETE CONGENITAL HEART BLOCK. REPORT OF 35 CASES J M Reid, E N Coleman, W Doig 236

ABSENT LEFT ATRIOVENTRICULAR CONNECTION WITH RIGHT ATRIUM CONNECTED TO MORPHOLOGICALLY LEFT VENTRICULAR CHAMBER, RUDIMENTARY RIGHT VENTRICULAR CHAMBER, AND VENTRICULOARTERIAL DISCORDANCE. PROBLEM OF MITRAL VERSUS TRICUSPID ATRESIA A Restivo, S Y Ho, R H Anderson, H Cameron, J L Wilkinson 240

TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION. REPAIR USING DEEP HYPOTHERMIA AND CIRCULATORY ARREST IN 44 CONSECUTIVE INFANTS
D F Dickinson, K M Parimelazhagan, M C K Tweedie, C R West, G P Piccoli, F Musumeci, D I Hamilton 249

ROUTINE RADIONUCLIDE TECHNIQUES IN EVALUATION OF PATIENTS WITH SUSPECTED CORONARY HEART DISEASE E Thaulow, K Rootwelt, J Erikssen, S Nitter-Hauge 255

REVERSIBLE ISCHAEMIA OF RIGHT VENTRICLE DETECTED BY EXERCISE THALLIUM-201 SCINTIGRAPHY A Lahiri, G P Carboni, J W Crawley, E B Raftery 260

CORONARY ARTERY NARROWING WITHOUT IRREVERSIBLE MYOCARDIAL DAMAGE OR DEVELOPMENT OF COLLATERALS. ASSESSMENT OF "CRITICAL" STENOSIS IN A HUMAN MODEL Erling Falk 265

CAPTOPRIL AS TREATMENT FOR PATIENTS WITH PULMONARY HYPERTENSION. PROBLEM OF VARIABILITY IN ASSESSING CHRONIC DRUG TREATMENT S Rich, J Martinez, W Lam, K M Rosen 272

LEFT VENTRICULAR FUNCTION IN HYPOTHYROIDISM. RESPONSES TO EXERCISE AND BETA ADRENOCEPTOR BLOCKADE J C Forfar, A L Muir, A D Toft 278

A TRIAL OF PROPHYLACTIC MEXILETINE IN HOME CORONARY CARE J A Bell, J M Thomas, J R Isaacson, N J C Snell, D W Holt 285

CASE REPORTS 291, 294, 298

CORRESPONDENCE 301

NOTICES 308

Number 4

EDITORIAL: EXERCISE HEART RATE/ST SEGMENT RELATION. PERFECT PREDICTOR OF CORONARY DISEASE? K M Fox 309

ACCURATE DETECTION OF CORONARY HEART DISEASE BY NEW EXERCISE TEST
M S Elamin, R Boyle, M M Kardash, D R Smith, J B Stoker, W Whitaker, D A S G Mary, R J Linden 311

SUPRASTERNAL CROSS-SECTIONAL ECHOCARDIOGRAPHY IN ASSESSMENT OF PATENT DUCTUS ARTERIOSUS J F Smallhorn, J C Huhta, R H Anderson, F J Macartney 321

CROSS-SECTIONAL ECHOCARDIOGRAPHIC ASSESSMENT OF CONDITIONS WITH ATRIOVENTRICULAR VALVE LEAFLETS ATTACHED TO THE ATRIAL SEPTUM AT THE SAME LEVEL
J F Smallhorn, G R Sutherland, R H Anderson, F J Macartney 331

EFFECT OF AGE RELATED CHANGES IN CHAMBER SIZE, WALL THICKNESS, AND HEART RATE ON LEFT VENTRICULAR FUNCTION IN NORMAL CHILDREN
M G St John Sutton, D L Marier, P J Oldershaw, R Sacchetti, D G Gibson 342

SERUM LEVELS OF ACUTE PHASE AND CARDIAC PROTEINS AFTER MYOCARDIAL INFARCTION, SURGERY, AND INFECTION F Voulgari, P Cummins, T I M Gardecki, N J Beeching, P C W Stone, J Stuart 352

VASOMOTOR WAVE AND BLOOD PRESSURE RESPONSE TO ERECT POSTURE AFTER OPERATION FOR AORTIC COARCTATION J Sehested, G Schultze 357

COMPARATIVE HAEMODYNAMIC DOSE RESPONSE EFFECTS OF PROPRANOLOL AND LABETALOL IN CORONARY HEART DISEASE B Silke, G I C Nelson, R C Ahuja, S H Taylor 364

POSTOPERATIVE THALLIUM-201 MYOCARDIAL IMAGES. EVIDENCE OF REGRESSION OF RIGHT VENTRICULAR HYPERTROPHY IN MAN
H Yamazaki, T Tsugu, S Handa, Y Takagi, F Ohsuzu, M Kondo, A Kubo, T Inoue, Y Nakamura 372

BLOOD PRESSURE AND HAEMODYNAMICS IN TEENAGERS
A Hofman, R C Ellison, J Newburger, O S Miettinen 377

EVALUATION OF DRUG-INDUCED CHANGES IN MYOCARDIAL REPOLARISATION USING THE PACED EVOKED RESPONSE R M Donaldson, A F Rickards 381

CROSS-SECTIONAL ECHOCARDIOGRAPHIC DIAGNOSIS OF SYSTEMIC VENOUS RETURN
J C Huhta, J F Smallhorn, F J Macartney, R H Anderson, M de Leval 388

SEVERE TRICUSPID STENOSIS PRESENTING AS TRICUSPID ATRESIA. ECHOCARDIOGRAPHIC DIAGNOSIS AND SURGICAL MANAGEMENT. D F Shore, M L Rigby, C Lincoln 404

CASE REPORTS 407, 410, 413

NOTICES 416

Number 5

EDITORIAL: THEORY AND PRACTICE IN PREVENTION OF ARTERIAL THROMBOSIS J R A Mitchell 417

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION COEXISTING WITH VENTRICULAR SEPTAL DEFECT
D F Shore, J Smallhorn, J Stark, C Lincoln, M R de Leval 421

TWO DIMENSIONAL ECHOCARDIOGRAPHIC ASSESSMENT OF AORTIC VALVE MORPHOLOGY: FEASIBILITY OF BICUSPID VALVE DETECTION. PROSPECTIVE STUDY OF 100 ADULT PATIENTS
M J Zema, M Caccavano 428

ECHOCARDIOGRAPHIC FEATURES OF EOSINOPHILIC ENDOMYOCARDIAL DISEASE
J Davies, D G Gibson, R Foale, K Heer, C J F Spry, C M Oakley, J F Goodwin 434

PHASE ANALYSIS OF THE FIRST PASS RADIONUCLIDE ANGIOCARDIOGRAM
S Walton, P J Ell, P H Jarritt, R H Swanton 441

LOCALISATION AND DIRECTION OF MITRAL REGURGITANT FLOW IN MITRAL ORIFICE STUDIED WITH COMBINED USE OF ULTRASONIC PULSED DOPPLER TECHNIQUE AND TWO DIMENSIONAL ECHOCARDIOGRAPHY
K Miyatake, Y Nimura, H Sakakibara, N Kinoshita, M Okamoto, S Nagata, K Kawazoe, T Fujita 449

ALTERNATING ATRIAL ELECTROMECHANICAL DISSOCIATION AS CONTRIBUTING FACTOR FOR PULSUS ALTERNANS F W A Verheugt, H Scheck, R S Meltzer, J Roelandt 459

LEFT AND RIGHT VENTRICULAR TRABECULAR PATTERNS. CONSEQUENCE OF VENTRICULAR SEPTATION AND VALVE DEVELOPMENT A C G Wenink, A C Gittenberger-de Groot 462

PERSISTENCE OF DUCTUS ARTERIOSUS WITH LEFT TO RIGHT SHUNT IN THE OLDER PATIENT
R M Marquis, H C Miller, R J M McCormack, M B Matthews, A H Kitchin 469

TRICUSPID ATRESIA: ANALYSIS OF CORONARY ARTERY DISTRIBUTION AND VENTRICULAR MORPHOLOGY J E Deanfield, G Tommasini, R H Anderson, F J Macartney 485

EFFECT OF NICOTINE ON PRODUCTION OF PROSTACYCLIN IN HUMAN UMBILICAL ARTERY
I Stoel, W J v d Giessen, E Zwolsman, F W A Verheugt, F ten Hoor, F J A Quadt, P G Hugenholtz 493

REMOVAL OF EMBOLISED CATHETERS USING FLEXIBLE ENDOSCOPY FORCEPS T R D Shaw 497

CASE REPORTS 501, 504, 507, 510

Number 6

TOTAL ANOMALOUS PULMONARY VENOUS RETURN. PRENATAL DAMAGE TO PULMONARY VASCULAR BED AND EXTRAPULMONARY VEINS Sheila G Haworth 513

COMPUTER ANALYSIS OF CARDIAC CONTRACTILITY VARIABLES OBTAINED BY M-MODE ECHOCARDIOGRAPHY IN NORMAL NEWBORNS R Hofstetter, A Mayr, G von Bernuth 525

CLINICAL, ECHOCARDIOGRAPHIC, AND OPERATIVE FINDINGS IN ACTIVE INFECTIVE ECHOCARDITIS T H Pringle, S W Webb, M M Khan, H O J O'Kane, J Cleland, A A J Adgey 529

PREOPERATIVE ECHOCARDIOGRAPHIC DIAGNOSIS OF ANTERIOR MITRAL VALVE LEAFLET FENESTRATION ASSOCIATED WITH INFECTIVE ENDOCARDITIS M Matsumoto, J Strom, H Hirose, H Abe 538

HAEMODYNAMIC AND HORMONAL EFFECTS OF CAPTOPRIL IN PRIMARY PULMONARY HYPERTENSION H Ikram, A H Maslowski, M G Nicholls, E A Espiner, F T L Hull 541

TRANSMURAL, HAEMORRHAGIC MYOCARDIAL INFARCTION AFTER INTRACORONARY STREPTOKINASE. CLINICAL, ANGIOGRAPHIC, AND NECROPSY FINDINGS D G Mathey, J Schofer, K-H Kuck, U Beil, G Klöppel 546

SUDDEN VERSUS GRADUAL WITHDRAWAL OF SOTALOL IN AMBULANT PATIENTS WITH ISCHAEMIC HEART DISEASE A Henderson, J Errington 552

PROJECTION OF ST SEGMENT CHANGES ON TO THE FRONT OF THE CHEST. PRACTICAL IMPLICATIONS FOR EXERCISE TESTING AND AMBULATORY MONITORING K M Fox, J Deanfield, P Ribero, D England, C Wright 555

PRECORDIAL ST SEGMENT DEPRESSION IN PATIENTS WITH INFERIOR MYOCARDIAL INFARCTION: CLINICAL IMPLICATIONS J S Gelman, A Saltups 560

COMPLETE TRANSPOSITION OF GREAT ARTERIES WITH COARCTATION OF AORTA O Milanesi, G Thiene, R M Bini, P A Pellegrino 566

ACCURACY AND RELIABILITY OF TWO INDIRECT AMBULATORY BLOOD PRESSURE RECORDERS: REMLER M2000 AND CARDIODYNE SPHYGMOLOG D J Fitzgerald, W G O'Callaghan, R McQuaid, K O'Malley, E O'Brien 572

NORMAL CORONARY ARTERIOGRAM. AN AVOIDABLE TEST? C Ilsley, A Stockley, D Clitsakis, C Layton 580

SINUS NODE FUNCTION IN FIRST THREE WEEKS AFTER CARDIAC TRANSPLANTATION A F Mackintosh, D J Carmichael, C Wren, R Cory-Pearce, T A H English 584

IRREVERSIBLE MORPHOLOGICAL CHANGES CONTRIBUTING TO DEPRESSED CARDIAC FUNCTION AFTER SURGERY FOR CHRONIC AORTIC REGURGITATION R M Donaldson, R Florio, A F Rickards, J G Bennett, M Yacoub, D N Ross, E Olsen 589

CASE REPORTS 598, 601

CORRESPONDENCE 604

NOTICES 606

INDEX 607

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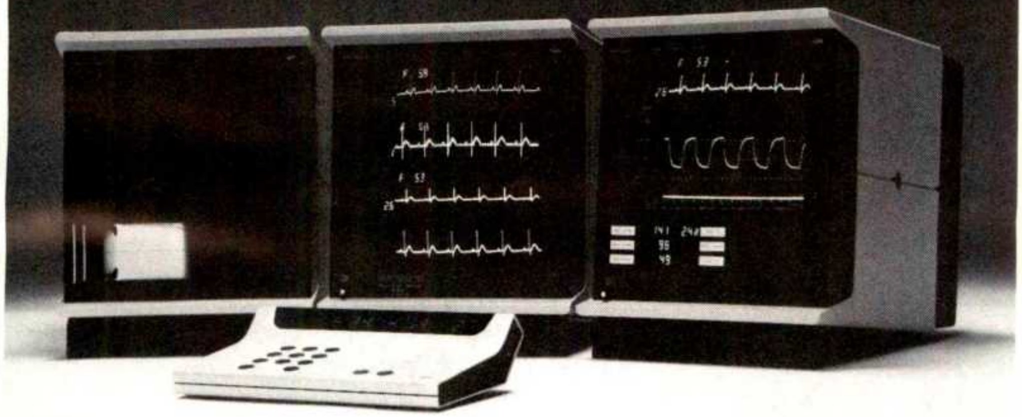

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Circulation

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Lewis A. Conner Memorial Lecture:

Choices That Must Not Be Made..
Richard D. Rem[illegible]

James B. Herrick Lecture:

Remarks on the Present State and Future of Academic Cardiology....
Eugene Braunwald

Current Topics:

Effects of Physical Training on Myocardial Vascularity and Perfusion
James Scheuer

Original Articles:

The Qt Interval Throughout the First 6 Months of Life: A Prospective Study..
Peter J. Schwartz, Massimo Montemerlo,
Mario Facchini, Patrizia Salice, Dario Rosti,
Gianluigi Poggio, and Roberto Giorgetti

Editorial: The QT Interval and Sudden Infant Death Syndrome ....
Warren G. Guntheroth

Treatment of Paroxysmal Supraventricular Tachycardia in Infancy with Digitalis, Adenosine-5'-Triphosphate, and Verapamil: A Comparative Study..
Raffaele Greco, Benito Musto, Vincenzo Arienzo,
Alfredo Alborino, Salvatore Garofalo, and
Federico Marsico

Clinical Presentation and Natural History of Mild Discrete Subaortic Stenosis. Follow-up of 1—17 Years..
Abraham Shem-Tov, Adam Schneeweis,
Michael Motro, and Henry N. Neufeld

Preoperative and Postoperative Renin Levels in Coarctation of the Aorta..
Frederick B. Parker, Jr., David H.P. Streeten,
Bruce Farrell, Marie S. Blackman,
Henry M. Sondheimer, and
Gunnar H. Anderson, Jr.

The Pressor Effect of Moderate Alcohol Consumption in Man: A search for Mechanisms ....
Peter D. Arkwright, Lawrence J. Beilin,
Robert Vandongen, Ian A. Rouse, and
Claire Lalor

Dietary Intake and Serum Total Cholesterol Level: Their Relationship to Different Lifestyles in Several Japanese Populations..............
Hirotsugu Ueshima, Minoru Iida,
Takashi Shimamoto, Masamitsu Konishi,
Masato Tanigaki, Mitsunori Doi,
Noriyuki Nakanishi, Yoshihiro Takayama,
Hideki Ozawa, and Yoshio Komachi

Prognostic Value of Exercise Testing, Coronary Angiography and Left Ventriculography 6—8 Weeks After Myocardial Infarction..........
P.J. De Feyter, M.J. van Eenige, D. H. Dighton,
F.C. Visser, J. de Jong, and J.P. Roos

Left Ventricular Myocardial Blood Flow in Multivessel Coronary Artery Disease..
Paul H. Chen, Allen B. Nichols, Melvin B. Weiss,
Robert R. Sciacca, Paul D. Walter,
and Paul J. Cannon

Pharmacologic Modification of Myocardial Ischemia..........................
Lewis Wetstein, Michael B. Simson,
Peter D. Feldman, and Alden H. Harken

Myocardial Lactate and Adenosine Metabolite Production As Indicators of Exercise-induced Myocardial Ischaemia in the Dog......
Thomas R. Vrobel, Charles R. Jorgensen,
and Robert J. Bache

Survival of Medically Treated Patients in the Coronary Artery Surgery Study (CASS) Registry..
Michael B. Mock, Ivar Ringqvist, Lloyd D. Fisher,
Kathryn B. Davis, Bernard R. Chaitman,
Nicholas T. Kouchoukos, George C. Kaiser,
Edwin Alderman, Thomas J. Ryan,
Richard O. Russell, Jr., Suzanne Mullin,
David Fray, Thomas Killip III, and Participants
in the Coronary Artery Surgery Study

Treatment of Stable Angina of Effort with Verapamil: A Double-blind, Placebo-controlled Randomized Crossover Study........................
Samuel J. Brodsky, Sally S. Cutler, Donald A. Weiner,
Carolyn H. McCabe, Thomas J. Ryan and
Michael D. Klein

A Double-blind Randomized Trial of Propranolol and Verapamil in the Treatment of Effort Angina...
Norman N. Sadick, Arthur T.H. Tan,
Peter J. Fletcher, John Morris, and
David T. Kelly

Effects of a Calcium-channel Antagonist on Large and Small Coronary Arteries in Conscious Dogs ....
Stephen F. Vatner and Thomas H. Hintze

Clinical Characteristics Associated with Sudden Death in Patients with Variant Angina..
D. Douglas Miller, David D. Waters,
Jadwiga Szlachcic, and Pierre Théroux

The Effect of Intraaortic Balloon Counterpulsation on Regional Myocardial Blood Flow and Oxygen Consumption in the Presence of Coronary Artery Stenosis in Patients with Unstable Angina....
David O. Williams, Kenneth S. Korr, Henry Gewirtz,
and Albert S. Most

Two-dimensional Echocardiography in Experimental Coronary Stenosis. I. Sensitivity and Specificity in Detecting Transient Myocardial Dyskinesis: Comparison with Sonomicrometers........
Natesa G. Pandian and Richard E. Kerber

Two-dimensional Echocardiography in Experimental Coronary Stenosis. II. Relationship Between Systolic Wall Thinning and Regional Myocardial Perfusion in Severe Coronary Stenosis.......
Natesa G. Pandian, Robert A. Kieso,
and Richard E. Kerber

A New Two-dimensional Echocardiographic Technique for Evaluating Right Ventricular Size and Performance in Patients with Obstructive Lung Disease..
Mark R. Starling, Michael H. Crawford,
Sherman G. Sorensen, and Robert A. O'Rourke

Postural Changes in Pulmonary Blood Flow in Pulmonary Hypertension: A Noninvasive Technique Using Ventilation-Perfusion Scans..
Matthew Horn, Wayne Hooper, Bernard Brach,
William Ashburn, and Kenneth Moser, with the
technical assistance of V. Sgvoi

Evaluation of Noninvasive Tests of Cardiac Damage in Suspected Cardiac Contusion...
Ralph T. Potkin, Jeffrey A. Werner,
Gene B. Trobaugh, Charles H. Chestnut III,
C. James Carrico, Alfred Hallstrom,
and Leonard A. Cobb

Indium-111-labeled Platelets: Effect of Heparin on Uptake by Venous Thrombi and Relationship to the Activated partial Thromboplastin Time...
Peter F. Fedullo, Kenneth M. Moser,
Kathleen S. Moser, Ronald Konopka,
and Michael T. Hartman

Effect of Exercise on Erythrocyte Count and Blood Activity Concentration After Technetium-99m In Vivo Red Blood Cell Labeling ..
Marvin A. Konstam, Sabah Tu'meh, Joshua Wynne,
J. Robert Beck, Joseph Kozlowski, and
B. Leonard Holman

Ejection Fraction Response to Exercise in Patients with Chest Pain, Coronary Artery Disease and Normal Resting Ventricular Function...
Raymond J. Gibbons, Kerry L. Lee,
Frederick R. Cobb, R. Edward Coleman,
and Robert H. Jones

Serial Thallium-201 Myocardial Imaging After Dipyridamole Infusion: Diagnostic Utility In Detecting Coronary Stenoses and Relationship to Regional Wall Motion ....

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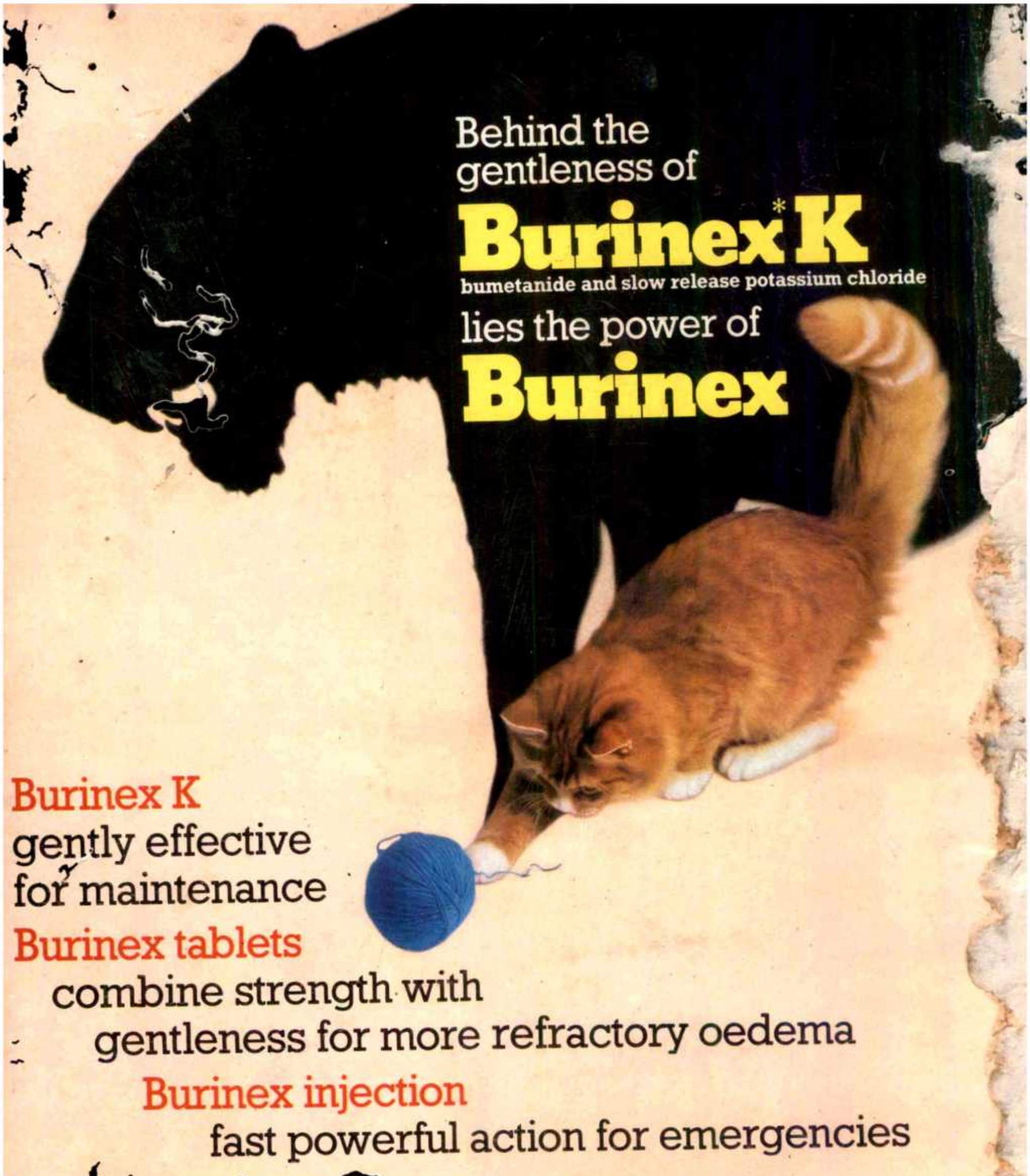

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